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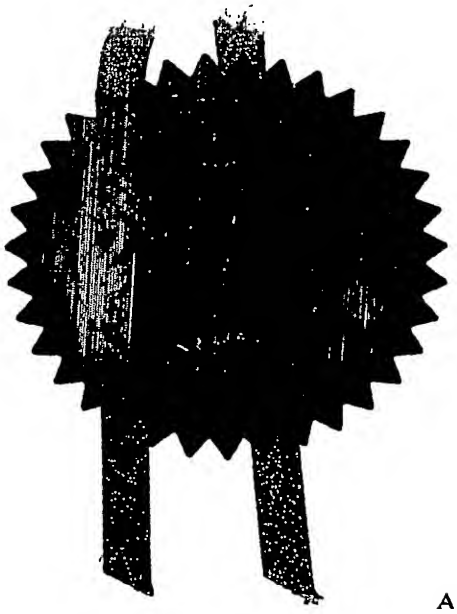

Signed R. Mahoney

Dated 4 July 2003

An Executive Agency

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P01/7700 0.00-0314698.2

Request for grant of a patent

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1. Your reference — MG/HG/PF4909P1

2. Patent application number
(The Patent Office will fill in his part) — 0314698.2 — 24 JUN 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — SmithKline Beecham Corporation
One Franklin Plaza, P.O. Box 7929, Philadelphia, Pennsylvania 19101, United States of America

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United States of America
5949497004

4. Title of the invention — Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* — 8072555004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
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Continuation sheets of this form	
Description	81
Claim(s)	3
Abstract	1
Drawings	

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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application
Signature M Gibson Date 24-Jun-03

12. Name and daytime telephone number of person to contact in the United Kingdom: M Gibson 01279 644841

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Compounds

This invention relates to novel heterocyclyl pyridine derivatives which are inhibitors of the transforming growth factor, ("TGF")-ß signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF-β type I or activin-like kinase ("ALK")-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway.

TGF-β1 is the prototypic member of a family of cytokines including the TGF-βs, activins, inhibins, bone morphogenetic proteins and Müllerian-inhibiting substance, that signal through a family of single transmembrane serine/threonine kinase receptors. These receptors can be divided in two classes, the type I or activin like kinase (ALK) receptors and type II receptors. The ALK receptors are distinguished from the type II receptors in that the ALK receptors (a) lack the serine/threonine rich intracellular tail, (b) possess serine/threonine kinase domains that are very homologous between type I receptors, and (c) share a common sequence motif called the GS domain, consisting of a region rich in glycine and serine residues. The GS domain is at the amino terminal end of the intracellular kinase domain and is critical for activation by the type II receptor. Several studies have shown that TGF-β signaling requires both the ALK and type II receptors. Specifically, the type II receptor phosphorylates the GS domain of the type I receptor for TGF-β, ALK5, in the presence of TGF-β. The ALK5, in turn, phosphorylates the cytoplasmic proteins smad2 and smad3 at two carboxy terminal serines. The phosphorylated smad proteins translocate into the nucleus and activate genes that contribute to the production of extracellular matrix. Therefore, preferred compounds of this invention are selective in that they inhibit the type I receptor and thus matrix production.

Activation of the TGF-β1 axis and expansion of extracellular matrix are early and persistent contributors to the development and progression of chronic renal disease and vascular disease. Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. Further, TGF-β1 plays a role in the formation of fibronectin and plasminogen activator inhibitor-1, components of sclerotic deposits, through the action of smad3 phosphorylation by the TGF-β1 receptor ALK5. Zhang Y., *et al*, *Nature*, 1998; 394(6696), 909-13; Usui T., *et al*, *Invest. Ophthalmol. Vis. Sci.*, 1998; 39(11), 1981-9.

Progressive fibrosis in the kidney and cardiovascular system is a major cause of suffering and death and an important contributor to the cost of health care. TGF-β1 has been implicated in many renal fibrotic disorders. Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. TGF-β1 is elevated in acute and chronic glomerulonephritis Yoshioka K., *et al*, *Lab. Invest.*, 1993; 68(2), 154-63, diabetic nephropathy Yamamoto, T., *et al*, 1993, *PNAS* 90, 1814-1818., allograft rejection, HIV nephropathy and angiotensin-induced nephropathy Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. In these diseases the levels of TGF-β1 expression coincide with the production of extracellular matrix. Three lines of evidence suggest a causal relationship between TGF-β1 and the production of matrix. First, normal glomeruli, mesangial cells and non-renal cells can be induced to produce extracellular-matrix protein and inhibit protease activity by exogenous TGF-β1 in vitro. Second, neutralizing anti-bodies against TGF-β1 can prevent the accumulation of extracellular matrix in nephritic rats. Third, TGF-β1 transgenic mice or in vivo transfection of the TGF-β1 gene into normal rat kidneys resulted in the rapid development of glomerulosclerosis. Kopp J.B., *et al*, *Lab. Invest.*, 1996; 74(6), 991-1003. Thus, inhibition of TGF-β1 activity is indicated as a therapeutic intervention in chronic renal disease.

TGF-β1 and its receptors are increased in injured blood vessels and are indicated in neointima formation following balloon angioplasty Saltis J., *et al*, *Clin. Exp. Pharmacol. Physiol.*, 1996; 23(3), 193-200. In addition TGF-β1 is a potent stimulator of smooth muscle cell ("SMC") migration in vitro and migration of SMC in the arterial wall is a contributing factor in the pathogenesis of atherosclerosis and restenosis. Moreover, in multivariate analysis of the endothelial cell products against total cholesterol, TGF-β receptor ALK5 correlated with total cholesterol ($P < 0.001$) Blann A.D., *et al*, *Atherosclerosis*, 1996; 120(1-2), 221-6. Furthermore, SMC derived from human atherosclerotic lesions have an increased ALK5/TGF-β type II receptor ratio. Because TGF-β1 is over-expressed in fibroproliferative vascular lesions, receptor-variant cells would be allowed to grow in a slow, but uncontrolled fashion, while overproducing extracellular matrix components McCaffrey T.A., *et al*, Jr., *J. Clin. Invest.*, 1995; 96(6), 2667-75. TGF-β1 was immunolocalized to non-foamy macrophages in atherosclerotic lesions where active matrix synthesis occurs, suggesting that non-foamy macrophages may participate in modulating matrix gene

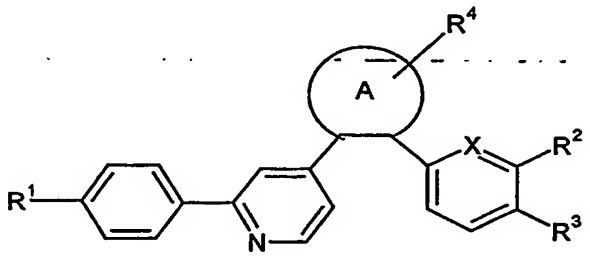
expression in atherosclerotic remodeling via a TGF-β-dependent mechanism. Therefore, inhibiting the action of TGF-β1 on ALK5 is also indicated in atherosclerosis and restenosis.

TGF-β is also indicated in wound repair. Neutralizing antibodies to TGF-β1 have been used in a number of models to illustrate that inhibition of TGF-β1 signaling is beneficial in restoring function after injury by limiting excessive scar formation during the healing process. For example, neutralizing antibodies to TGF-β1 and TGF-β2 reduced scar formation and improved the cytoarchitecture of the neodermis by reducing the number of monocytes and macrophages as well as decreasing dermal fibronectin and collagen deposition in rats Shah M., *J. Cell. Sci.*, 1995, 108, 985-1002. Moreover, TGF-β antibodies also improve healing of corneal wounds in rabbits Moller-Pedersen T., *Curr. Eye Res.*, 1998, 17, 736-747, and accelerate wound healing of gastric ulcers in the rat, Ernst H., *Gut*, 1996, 39, 172-175. These data strongly suggest that limiting the activity of TGF-β would be beneficial in many tissues and suggest that any disease with chronic elevation of TGF-β would benefit by inhibiting smad2 and smad3 signaling pathways.

TGF-β is also implicated in peritoneal adhesions Saed G.M., *et al*, *Wound Repair Regeneration*, 1999 Nov-Dec, 7(6), 504-510. Therefore, inhibitors of ALK5 would be beneficial in preventing peritoneal and sub-dermal fibrotic adhesions following surgical procedures.

Surprisingly, it has now been discovered that a class of novel heterocyclylpyridine derivatives function as potent and selective non-peptide inhibitors of ALK5 kinase and therefore, have utility in the treatment and prevention of various disease states mediated by ALK5 kinase mechanisms, such as chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis, and restenosis.

According to a first aspect, the invention provides a compound of formula (I), a pharmaceutically acceptable salt, solvate or derivative thereof:



(I)

wherein

A is selected from the list: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, indazole, imidazopyridine, quinazoline, quinoline, isoquinoline, pyrazole and triazole;

X is N or CH;

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo, cyano, perfluoro C_{1-6}alkyl, perfluoroC_{1-6}alkoxy, $-NR^5R^6$, $-(CH_2)_nNR^5R^6$, $-O(CH_2)_nOR^7$, $-O(CH_2)_n$-Het, $-O(CH_2)_nNR^5R^6$, $-CONR^5R^6$, $-CO(CH_2)_nNR^5R^6$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NR^5SO_2R^7$, $-NR^5COR^7$ and $-O(CH_2)_nCONR^5R^6$;

R^2 is selected from hydrogen, C_{1-6}alkyl, halo, cyano or perfluoroC_{1-6}alkyl;

R^3 is selected from hydrogen or halo;

R^4 is selected from hydrogen, halo, phenyl, C_{1-6}alkyl or $-NR^5R^6$;

where

R^5 and R^6 are independently selected from hydrogen; C_{1-6}alkyl optionally substituted by amino, monoC_{1-6}alkylamino, diC_{1-6}alkylamino, Het, alkoxy or cyano; Het; and C_{3-6}cycloalkyl optionally substituted by C_{1-6}alkyl; or R^5 and R^6 together with the nitrogen atom to which they are attached form a 3, 4, 5, 6 or 7-membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), cyano, $-CF_3$, hydroxy, $-OCF_3$, C_{1-6}alkyl and C_{1-6}alkoxy;

R^7 is selected from hydrogen and C_{1-6}alkyl;

Het is a 5 or 6-membered heterocyclyl group which may be saturated, unsaturated or aromatic, which may contain one or more heteroatoms selected from N, S or O and which may be substitued by C_{1-6}alkyl; and

n is 1-4;

with the provisos that :

a) when A is thiazole (wherein the thiazole sulfur is on the same side as the 4-pyridyl moiety); X is N; R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, cyano, perfluoroC_{1-6}alkyl or perfluoroC_{1-6}alkoxy; R^2 is hydrogen, C_{1-6}alkyl, halo, cyano or perfluoroC_{1-6}alkyl; and R^3 is hydrogen or halo; then R^4 is not NH_2,

b) when X is N, A is pyrazole (where the ring containing X is attached to the pyrazole ring at carbon atom next to a pyrazole ring nitrogen), R^2 is hydrogen then R^3 is not hydrogen.

According to a second aspect, the invention provides a compound of formula (I), a pharmaceutically acceptable salt, solvate or derivative thereof,

wherein

X is N or CH;

A is selected from the list: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, indazole, imidazopyridine, quinazoline, quinoline, isoquinoline and triazole;

R^1 is selected from H, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo, cyano, perfluoro C_{1-6}alkyl, perfluoroC_{1-6}alkoxy, $-NR^5R^6$, $-(CH_2)_nNR^5R^6$, $-O(CH_2)_nOR^5$, $-O(CH_2)_nNR^5R^6$, $-CONR^5R^6$, $-CO(CH_2)_nNR^5R^6$, $-SO_2R^5$, $-SO_2NR^5R^6$, $-NR^5SO_2R^5$ and $-NR^5COR^6$;

R^2 is selected from H, C_{1-6}alkyl, halo, CN or perfluoroC_{1-6}alkyl;

R^3 is selected from H or halo;

R^4 is selected from H, halo, C_{1-6}alkyl or $-NR^5R^6$;

R^5 and R^6 are independently selected from H or C_{1-6}alkyl; or R^5R^6 together with the atom to which they are attached form a 3, 4, 5, 6 or 7-membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl and C_{1-6} alkoxy; and

n is 1-4;

with the provisos that:

a) when A is thiazole (wherein the thiazole sulfur is on the same side as the 4-pyridyl moiety); X is N; R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, cyano, perfluoroC_{1-6}alkyl or perfluoroC_{1-6}alkoxy; R^2 is hydrogen, C_{1-6}alkyl, halo, cyano or perfluoroC_{1-6}alkyl; and R^3 is hydrogen or halo; then R^4 is not NH_2;

b) when X is N, A is pyrazole (where the ring containing X is attached to the pyrazole ring at carbon atom next to a pyrazole ring nitrogen), R^2 is hydrogen then R^3 is not hydrogen.

The following preferences apply to any one of the four aspects described hereinabove.

Preferably, A is selected from furan, thiophene, pyrrole, imidazole, pyridine, pyrimidine, oxazole, isoxazole, thiazole, isothiazole, thiadiazole, imidazopyridine, pyrazole and triazole, each of which may be optionally substituted by one or more of the substituents R^4.

More preferably, A is selected from triazole, imidazopyridine, thiazole, imidazole and pyrazole, each of which may be optionally substituted by one or more of the substituents R^4.

More preferably A is imidazole.

Preferably X is N.

Preferably R^2 is hydrogen, C_{1-6}alkyl or fluoro. More preferably R^2 is hydrogen or methyl. More preferably still, R^2 is methyl.

Preferably R^3 is hydrogen.

Preferably, when X is N, R^2 is methyl. More preferably when Y is N and R^2 is methyl, R^3 is hydrogen.

Preferably R^4 is hydrogen, phenyl, C_{1-6}alkyl or halo. More preferably, H, methyl or chloro.

Preferably when A is imidazole, R^4 is tert-butyl, isopropyl or methyl.

Preferably, R^5 and R^6 are independently H or methyl, or R^5R^6 together with the atom to which they are attached form a 3, 4, 5, 6 or 7 membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substitutents selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-4} alkyl and C_{1-4} alkoxy.

Suitably, R^5 and R^6 together with the atom to which they are attached form a morpholine, piperidine, pyrrolidine, piperazine, N-methyl piperazine, imidazole or N-methyl imidazole ring.

It will be appreciated that the present invention is intended to include compounds having any combination of the preferred groups listed hereinbefore.

Compounds of formula (I) which are of special interest as agents useful in the treatment or prophylaxis of disorders characterised by the overexpression of TGF-β are selected from the list:

4-{2-*tert*-Butyl-5-[6-methyl]-pyridin-2-yl-1*H*-imidazol-4-yl}-2-(4-methanesulfonyl-phenyl)-pyridine (Example 4A);

4-{4-[4-(2-*tert*-Butyl-5-{6-methyl}-pyridin-2-yl-1*H*-imidazol-4-yl)-pyridin-2-yl]-phenyl}-morpholine (Example 6A);

N-(tetrahydropyran-4-yl)-4-(4-{2-isopropyl-5-[6-methyl-pyridin-2-yl]-1*H*-imidazol-4-yl}-pyridin-2-yl)-benzamide (Example 15A);

4-{4-[4-(2-isopropyl-5-{6-methyl}-pyridin-2-yl-1*H*-imidazol-4-yl)-pyridin-2-yl]-phenyl}-morpholine (Example 16A);

4-(4-{4-[2-Isopropyl-5-(6-methyl-pyridin-2-yl)-1*H*-imidazol-4-yl]-pyridin-2-yl}-benzyl)-dimethyl-amine (Example 24A);

4-(4-{4-[2-Isopropyl-5-(6-methyl-pyridin-2-yl)-1*H*-imidazol-4-yl]-pyridin-2-yl}-benzyl)-morpholine (Example 23A);

N-(tetrahydropyran-4-yl)-4-(4-{2-*tert*-Butyl-5-[6-methyl-pyridin-2-yl]-1*H*-imidazol-4-yl}-pyridin-2-yl)-benzamide (Example 1A);

(4-{4-[2-*tert*-Butyl-5-(6-methyl-pyridin-2-yl)-1*H*-imidazol-4-yl]-pyridin-2-yl}-benzyl)-pyrrolidine (Example 22A);

4-(2-*tert*-Butyl-5-{6-methyl}-pyridin-2-yl-1*H*-imidazol-4-yl)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridine (Example 27A); and

4-{4-[4-(2-methyl-5-{6-methyl}-pyridin-2-yl-1*H*-imidazol-4-yl)-pyridin-2-yl]-phenyl}-morpholine (Example 17A);

and pharmaceutically acceptable salts, solvates and derivatives thereof.

The term "C_{1-6}alkyl" as used herein, whether on its own or as part of a group, refers to a straight or branched chain saturated aliphatic hydrocarbon radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl and hexyl.

The term "alkenyl" as a group or part of a group refers to a straight or branched chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number(s) of carbon atoms. References to "alkenyl" groups include groups which may be in the E- or Z-form or mixtures thereof.

The term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy.

The term "perfluoroalkyl" as used herein includes compounds such as trifluoromethyl.

The term "perfluoroalkoxy" as used herein includes compounds such as trifluoromethoxy.

The terms "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of posssible substituents, those substituents may be the same or different.

As used herein the term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the compound of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) the a compound of formula (I) or an active metabolite or residue thereof, eg, a prodrug. Preferred pharmaceutically acceptable derivatives according to the invention are any pharmaceutically acceptable salts, solvates or prodrugs.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di- basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like. Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Hereinafter, compounds, their pharmaceutically acceptable salts, their solvates and polymorphs, defined in any aspect of the invention (except intermedate compounds in chemical processes) are referred to as "compounds of the invention".

Compounds of the invention may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

The term "ALK5 inhibitor" is used herein to mean a compound, other than inhibitory smads, e.g. smad6 and smad7, which selectively inhibits the ALK5 receptor preferentially over p38 or type II receptors.

The term "ALK5 mediated disease state" is used herein to mean any disease state which is mediated (or modulated) by ALK5, for example a disease which is modulated by the inhibition of the phosphorylation of smad 2/3 in the TGF-1ß signaling pathway.

The term "ulcers" is used herein to include, but not to be limited to, diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers.

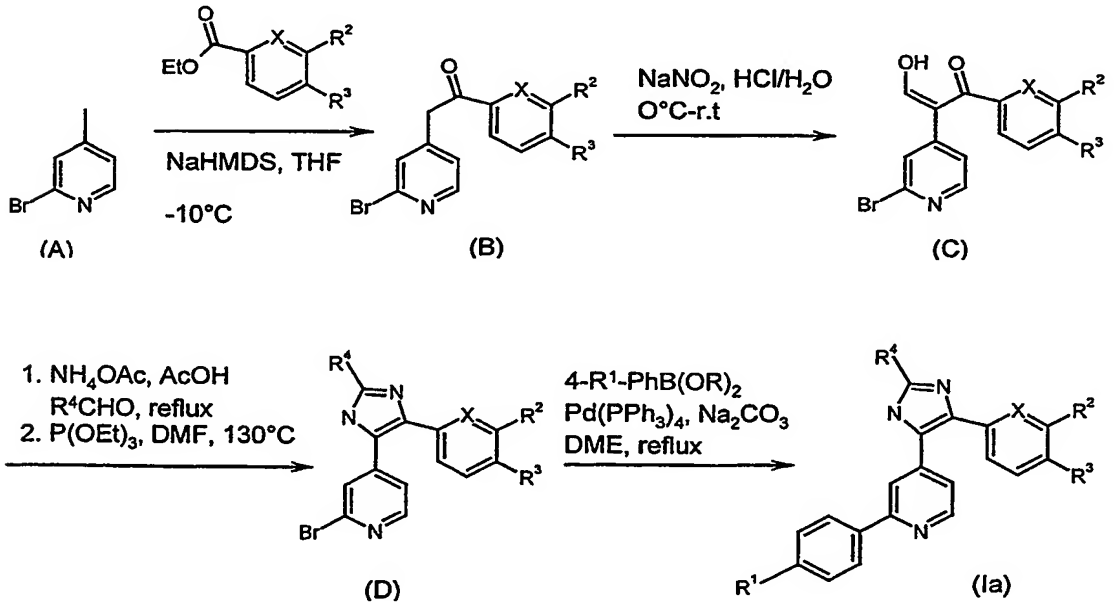
The compounds of the invention can be prepared by art-recognised procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

Compounds of the invention may be prepared, in known manner in avariety of ways. In the following reaction schemes and hereafter, unless otherwise stated R^1 to R^5, X and n are as defined in the first aspect. These processes form further aspects of the invention.

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc. Subsets of these general formulae are defined as (Ia), (Ib), (Ic) etc .... (IVa), (IVb), (IVc) etc.

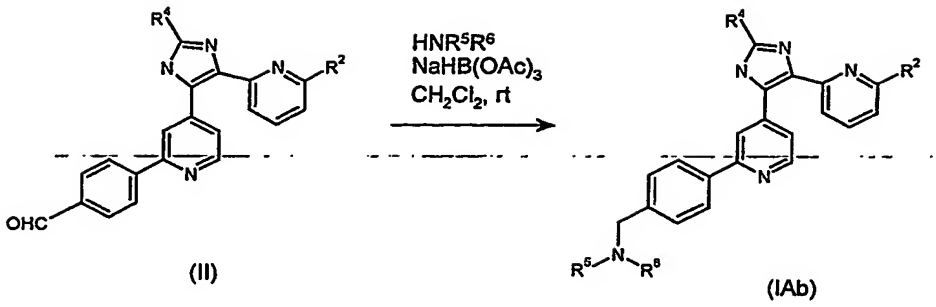
Compounds of formula (Ia), i.e. compounds of general formula (I) where A is imidazole, may be prepared according to Scheme 1. Ketones (B) may be treated with sodium nitrite in HCl to give α-oximinoketones (C) which may then be condensed with a suitably substituted aldehyde and ammonium acetate to give N-hydroxyimidazoles. Treatment of these derivatives with triethylphosphite gives compounds of formula (D) according to the method outlined in US Pat. 5,656,644. Boronic acid coupling gives compounds of formula (Ia). Preferred coupling conditions are those developed by Miyaura et al (Chem.Rev. 1995, 95: 2457), typically comprising reaction in an inert solvent in the presence of a base and a palladium or nickel catalyst at temperature between room temperature and 130°C for a period between 30 minutes and 48hours. Suitable bases include sodium carbonate, potassium carbonate, potassium hydroxide, sodium hydroxide. Suitable catalysts include tetrakis(triphenlyphosphine) palladium(0), palladium(II) acetate, dichlorobis(triphenylphosphine) palladium(II), tris(dibenylideneacetone) dipalladium(0) and dichlorobis(triphenylphosphine) nickel.

Scheme 1



Compounds of formula (IAb), i.e. compounds of formula (I) where A is imidazole, X is N, R^1 is $-CH_2NR^5R^6$ and R^3 is hydrogen, may be prepared in one step according to scheme 2.

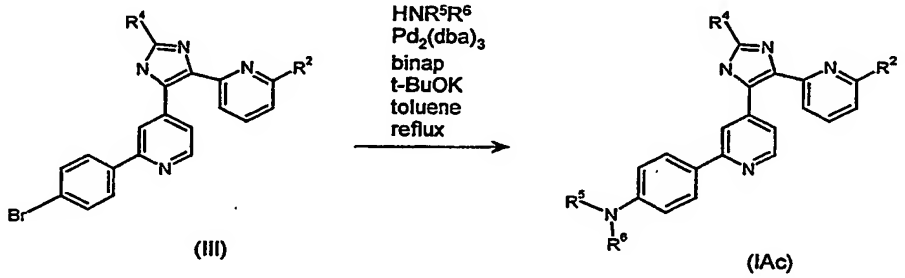
Scheme 2



(II) (IAb)

Compounds of formula (IAc), i.e. compounds of formula (I) where A is imidazole, X is N, R^1 is $-NR^5R^6$, may be prepared according to reaction scheme 3 by reacting compounds of formula (III) with HNR^5R^6 in the presence of a catalyst system preferably bis (dibenzylidene acetone)palladium and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (Binap) in potassium tert-butoxide in a suitable solvent such as toluene at elevated temperature.

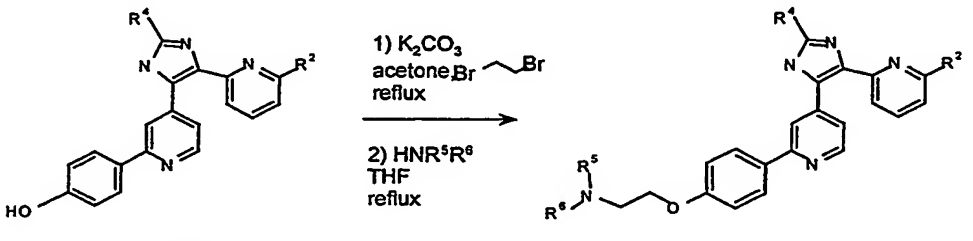
Scheme 3



(III) (IAc)

Compounds of formula (IAd), i.e. compounds of formula (I) where A is imidazole, X is N, R^1 is $-OCH_2CH_2NR^5R^6$, may be prepared according to reaction scheme 4 by reacting compounds of formula (IV) with 1,2-dibromoethane in the presence of a base preferably potassium carbomate in a suitable solvent, such as acetone, at elevated temperature. Treatment with HNR^5R^6 in a suitable solvent such as tetrahydrofuran at elevated temperature gives (IAd).

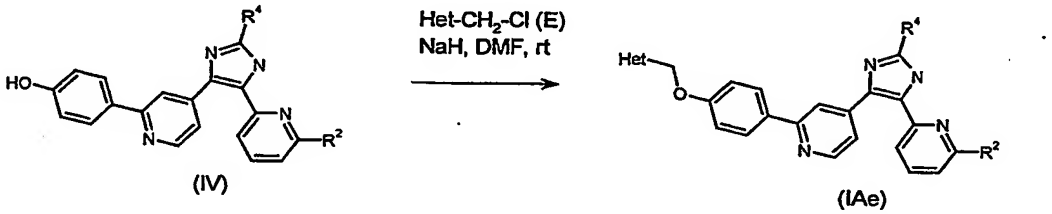
Scheme 4



(IV) (IAd)

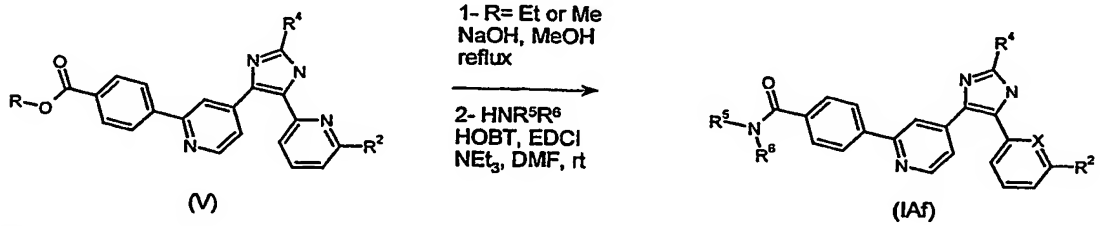
Compounds of formula (IAe), i.e. compounds of formula (I) where A is imidazole, X is N, R^1 is $-O(CH_2)_n$-Het and n is 1, may be prepared according to reaction scheme 5 by reacting compounds of formula (IV) with compounds of formula (E) in the presence of a base preferably sodium hydride in a suitable solvent, such as DMF, at room temperature.

Scheme 5



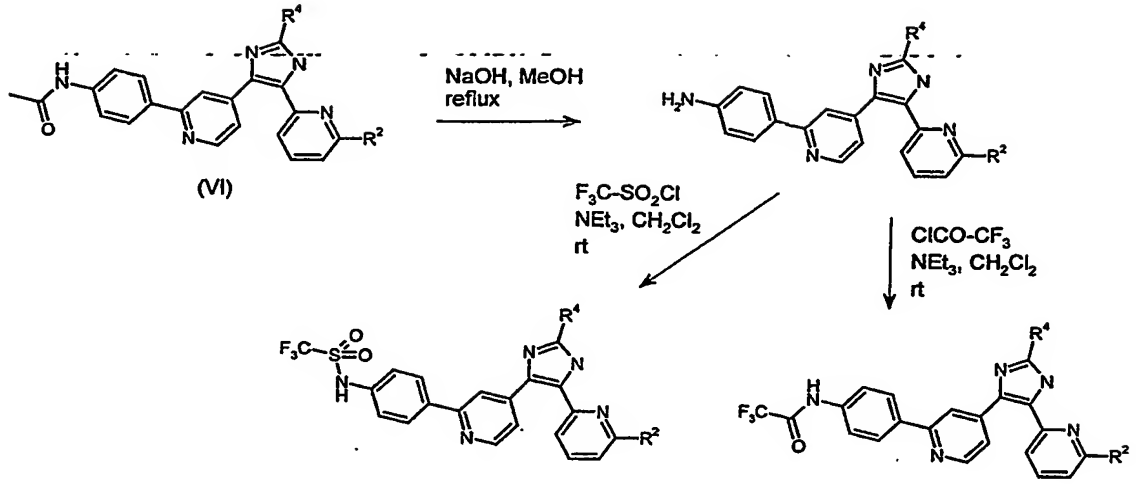
Compounds of formula (IAf), i.e. compounds of general formula (I) where A is imidazole, X is N and R^1 is $-CONR^5R^6$, may be prepared according to reaction scheme 6. Compounds of formula (V) (where R is methyl or ethyl), are firstly saponified by heating with sodium hydroxide in methanol, followed by conversion of the resulting carboxylic acid to amide (IAf). Preferred reaction conditions comprise treating the intermediate carboxylic acid with HNR^5R^6 in the presence of hydroxybenzotriazole (HOBT), 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and a suitable base such as triethylamine in a suitable solvent such as dimethylformamide at room temperature.

Scheme 6



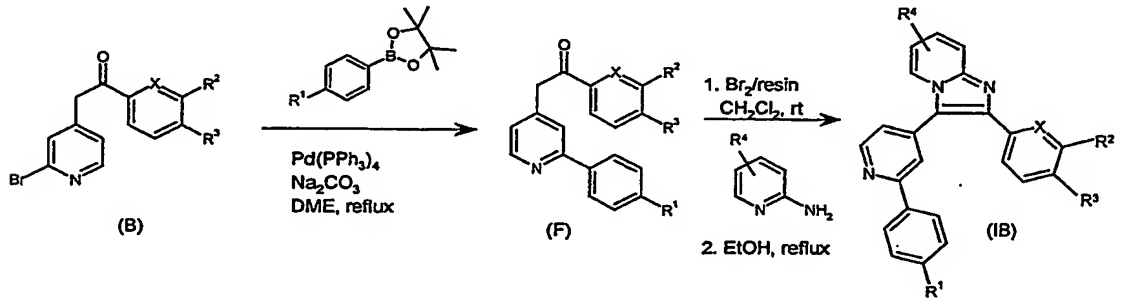
Compounds of general formula (I), where A is imidazole, X is N, R^1 is $-NHSO_2CF_3$ or $-NHCOCF_3$, may be prepared from common intermediates of formula (VI) according to reaction scheme 7. Firstly the acetyl group is removed from compounds of formula (VI) by treatment with sodium hydroxide in methanol at elevated temperature. The resulting amine is then treated with CF_3SO_2Cl or CF_3COCl preferably in the presence of a base such as triethylamine in a suitable solvent such as dicloromethane at room temperature.

Scheme 7



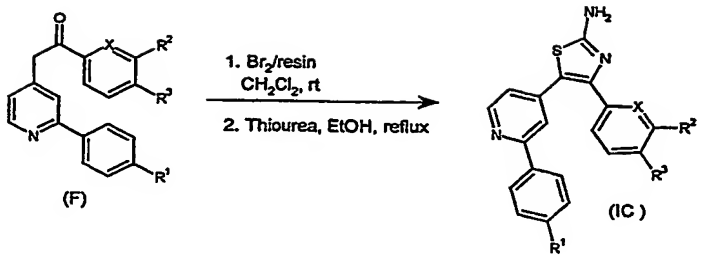
Compounds of formula (IB), i.e. compounds of general formula (I) where A is imidazopyridine, may be prepared according to the general method described in scheme 8.

Scheme 8



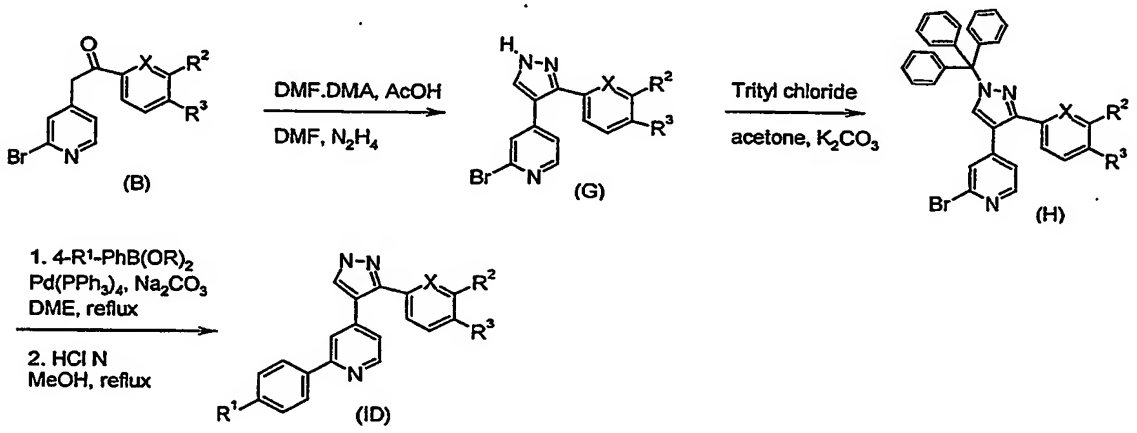
Compounds of formula (IC), i.e. compounds of general formula (I) where A is thiazole and R^4 is NH_2, may be prepared according to the general method described in scheme 9.

Scheme 9



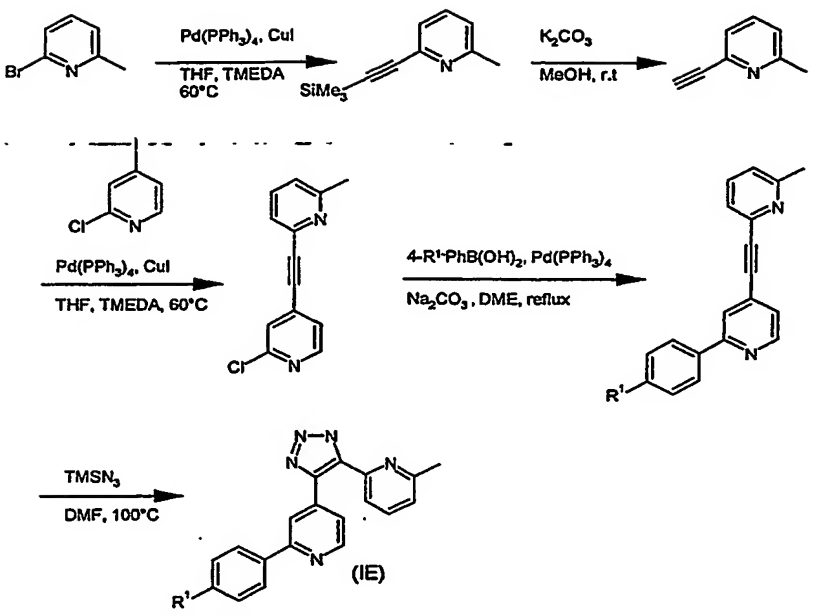
Compounds of formula (ID), i.e. compounds of general formula (I) where A is pyrazole and R^4 is H, may be prepared according to the general method described in scheme 10.

Scheme 10



Compounds of formula (ID), i.e. compounds of general formula (I) where A is triazole and R^4 is H, may be prepared according to the general method described in scheme 11.

Scheme 11



Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of the invention may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds. Libraries of compounds of the invention may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect there is provided a compound library comprising at least 2 compounds of the invention.

The compounds of the invention have been found to inhibit phosphorylation of the Smad-2 or Smad-3 proteins by inhibition of the TGF-β type I (ALK5) receptor.

The compounds of the invention have been tested in the assays described herein and have been found to be of potential therapeutic benefit in the treatment and prophylaxis of disorders characterised by the overexpression of TGF-β. Thus, there is provided a compound of the invention, for use as a medicament in human or veterinary medicine, particularly in the treatment or prophylaxis of disorders characterised by the overexpression of TGF-β.

It will be appreciated that references herein to treatment extend to prophylaxis as well as the treatment of established conditions. It will further be appreciated that references herein to treatment or prophylaxis of disorders characterised by the overexpression of TGF-β, shall include the treatment or prophylaxis of TGF-β associated disease such as fibrosis, especially liver and kidney fibrosis, cancer development, abnormal bone function and inflammatory disorders, and scarring.

Other pathological conditions which may be treated in accordance with the invention have been discussed in the introduction hereinbefore. The compounds of the present invention are particularly suited to the treatment of fibrosis and related conditions.

Compounds of the present invention may be administered in combination with other therapeutic agents, for example antiviral agents for liver diseases, or in combination with ACE inhibitors or angiotensin II receptor antagonists for kidney diseases.

According to a further aspect of the present invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the ALK5 receptor in mammals.

ALK5-mediated disease states, include, but are not limited to, chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis, kidney fibrosis, liver fibrosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis, keloids and restenosis.

According to a further aspect of the present invention there is provided a method of inhibiting the TGF-ß signaling pathway in mammals, for example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor.

According to a further aspect of the present invention there is provided a method of inhibiting matrix formation in mammals by inhibiting the TGF-β signalling pathway, for

example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor.

The compounds of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or diluent.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica;

disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when a compound of the invention is administered in the above-mentioned dosage range.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It will be appreciated that the invention includes the following further aspects. The preferred embodiments described for the first aspect extend these further aspects:

i) a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or diluent;

ii) the use of a compound of the invention in the manufacture of a medicament for the treatment or prophylaxis of a disorder characterised by the overexpression of TGF-β;

iii) the use of a compound of the invention in the manufacture of a medicament for the treatment or prophylaxis of a disorder mediated by the ALK5 receptor in mammals;

iv) the use of a compound of the invention in the manufacture of a medicament for the treatment or prophylaxis of a disorder selected from chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis, kidney fibrosis, liver fibrosis [for example, hepatitis B virus (HBV), hepatitis C virus (HCV)], alcohol induced hepatitis, retroperitoneal fibrosis, mesenteric fibrosis, haemochromatosis and primary biliary cirrhosis, endometriosis, keloids and restenosis; and

v) the use of a compound of the invention in the manufacture of a medicament for the treatment or prophylaxis of kidney fibrosis;

vi) a compound of the invention for use as a medicament;

vii) a method of treatment or prophylaxis of a disorder selected from chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis, kidney fibrosis, liver fibrosis [for example, hepatitis B virus (HBV), hepatitis C virus (HCV)], alcohol induced hepatitis, retroperitoneal fibrosis, mesenteric fibrosis, haemochromatosis and primary biliary cirrhosis, endometriosis, keloids and restenosis, in mammals, which comprises administration to the mammal in need of such treatment, an effective amount of a compound of the invention; and

viii) a combination of a compound of the invention with an ACE inhibitor or an angiotensin II receptor antagonist.

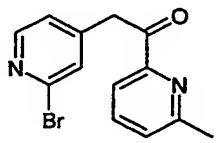
The following non-limiting examples illustrate the present invention.

Abbreviations

Binap	- 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
CH_2Cl_2	- dichloromethane
DME	- 1,2-Dimethoxyethane
DMF	- dimethylformamide
DMSO	- dimethylsulfoxide
EDCI	- 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
EtOAc	- ethyl acetate
EtOH	- ethanol
Et_3N	- triethylamine
HOBT	- hydroxybenzotriazole
MeOH	- methanol
NaH	- sodium hydride
$NaHCO_3$	- sodium hydrogen carbonate
Na_2CO_3	- sodium carbonate
$NaNO_2$	- sodium nitrite
Na_2SO_4	- sodium sulfate
NH_4Cl	- ammonium chloride
$Pd_2(dba)_3$	- tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_4$	- tetrakis(triphenylphosphine) palladium (0)
PTSA	- para-toluenesulfonic acid
t-BuOK	- potassium *tert*-butoxide
TEA	- triethylamine
TMEDA	- N,N,N',N'- tetramethylethylenediamine
THF	- tetrahydrofuran

Experimental for Imidazoles (A)

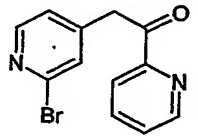
Intermediate 1A: 2-[2-Bromo-pyridin-4-yl]-1-(6-methyl-pyridin-2-yl)-ethanone



To a solution of 2-bromo-4-methyl-pyridine (5 g, 29mmol) in dry THF (70 ml), a solution of sodium bis-(trimethylsilyl)amide 2M in THF (32 ml, 2.2eq) was

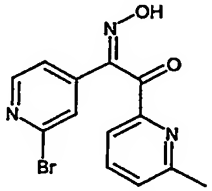
added dropwise at –30°C under nitrogen. The mixture was stirred at –30°C for 1h, then 6-methylpicolinic acid methyl ester (4.82 g, 32.3mmol, 1.1eq) was added. The reaction mixture was stirred at room temperature overnight. Diethyl ether was added and the precipitated solid filtered and washed with diethyl oxide. The solid was then diluted with saturated NH_4Cl solution and the aqueous phase extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated. The resulting orange powder was washed with pentane to give the title compound as a yellow solid (5.84 g, 70%); MS (APCI) : 292 (MH+).

Intermediate 2A: 2-(2-Phenylpyridin-4-yl)-1-pyridin-2-yl-ethanone



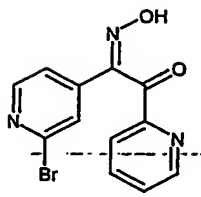
The title compound was obtained as a yellow solid (33.97g, 99.66%) from 2-bromo-4-methyl-pyridine and ethyl picolinate as described for intermediate1A; m.p. 111.2°C.

Intermediate 3A: 2-Hydroximino-2-[2-Bromo-pyridin-4-yl]-1-(6-methyl-pyridin-2-yl)-ethan-1-one



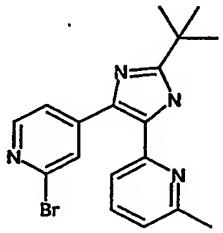
A solution of intermediate 1A (20g, 68.7mmol) in aqueous HCl 18% (360ml) was cooled at 0°C using a dry ice bath. To this solution was added sodium nitrite (5.6g, 82.44mmol), the reaction temperature was maintained at 0°C during this addition. After addition was complete, the dry ice bath was removed and the reaction mixture allowed to warm and stirred at room temperature for 30min. The reaction mixture was basified with aqueous NaOH (35%). The resulting precipitate was filtered off, washed with water and dried to give the title compound (mixture of two isomers) as a pink solid (20.53g, 93%); (MS APCI) m/z 321 (M+1).

Intermediate 4A: 2-Hydroximino-2-[2-Bromo-pyridin-4-yl]-1-(pyridin-2-yl)-ethan-1-one



The title compound was obtained as a solid (36g, 98%) from intermediate 2A and sodium nitrite as described for intermediate 3A; m.p : 200°C; MS APCI m/z 307 (M+1).

Intermediate 5A : 2-tert-butyl-4-(6-methyl-pyridin-2-yl)-5-(2-bromo-pyridin-4-yl)-imidazole



Intermediate 3A (6g, 18.7mmol) was dissolved in acetic acid (50mL) and treated with ammonium acetate (4.33g, 56.1mmol) and pivalaldehyde (2.7g, 37.4mmol). The resulting mixture was heated at reflux for 1h. On cooling the mixture was concentrated. The residue was dissolved in water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in DMF (60mL), treated with triethyl phosphite (2.78mL, 16.21mmol) and the resulting mixture was heated at 130°C for 5 h. To complete the reaction further triethyl phosphite (0.2eq) was added and the mixture was stirred at 130°C for 18h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was precipitated with diisopropyl ether to afford the title compound as a brown solid (3.88g, 65%); m.p. 200°C; (MS APCI) m/z 372 (M+1).

The following compounds of formula (D) were prepared using analogous methods to Intermediate 5A using the starting materials indicated in Table 1.

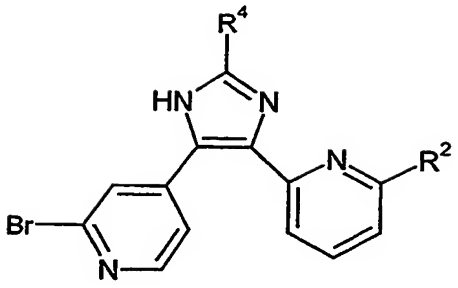
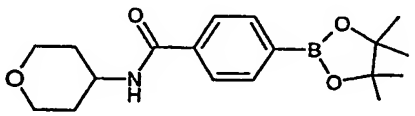


Table 1

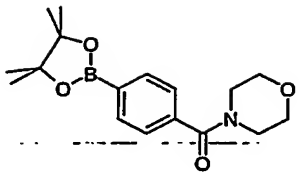
Int	R^2	R^4	Start. Material	Data
6A	H	t-Bu	4A	(MS, APCI) m/z 358 (M+1)
7A	Me	i-Pr	3A	(MS, APCI) m/z 358 (M+1)
8A	H	i-Pr	4A	M.p. 108°C; (MS, APCI) m/z 343-345 (M+1)
9A	Me	Me	3A	(MS, APCI) m/z 330 (M+1)

Intermediate 10A: N-(tetrahydropyran-4-yl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzamide



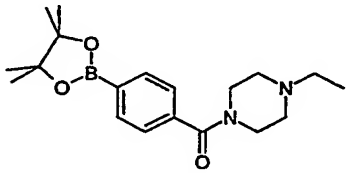
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (10g, 40mmol) was treated with thionyl chloride (25ml) at reflux for 2h. The mixture was concentrated to dryness under reduced pressure. The residue was diluted with toluene and the misxture was evaporated to dryness under reduced pressure. The acid chloride was then added at 5°C to a solution of 4-aminotetrahydropyran hydrochloride (5.52g, 40mmol) and triethylamine (12.2g, 120mmol) in CH_2Cl_2 .The reaction mixture was stirred at room temperature overnight. The resulting precipitate was filtered off and washed with diisopropyl oxide to give a first batch of compound. The filtrate was concentrated under reduced pressure and partitioned between water and CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give a second batch of compound. Solids were combined and washed with diisopropyl oxide to afford the title compound as a solid (12.5g, 37.88%); m.p. 258°C; (MS, APCI) m/z 332(M+1).

Intermediate 11A: N-[(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl)carbonyl]-morpholine



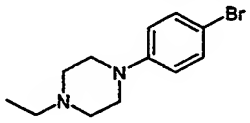
To a solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzoic acid (5g, 20.15 mmol) in a mixture CH_2Cl_2/DMF (50ml/5ml) were added morpholine (2.1ml, 24.2mmol), HOBT (3.3g, 24.2mmol), EDCI (4.65g, 24.2mmol) and triethylamine (4.2ml, 30.2mmol). The reaction mixture was stirred at room temperature for 3 days. The reaction mixture was partitioned between water and CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. After trituration with diisopropyl oxide, the title compound was obtained as a white solid (4.21g, 66%); ^1H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.80 (d, 2H), 7.40 (d, 2H), 3.70 (m, 4H), 3.55 (m, 2H), 3.35 (m, 2H), 1.30 (s, 12H).

Intermediate 12A: 1-Ethyl-4-[(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl)carbonyl]-piperazine



4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (8.24g, 33.22 mmol) and N-ethylpiperazine (5.1ml, 39.87mmol) were reacted as described for intermediate 11A to afford, after chromatography on silica gel (CH_2Cl_2/MeOH, 95/5), the title compound as a pale yellow oil which crystallised (9.64g, 84%); [MS APCI] m/z 345 (M+1).

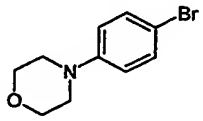
Intermediate 13A: 1-Ethyl-4-bromophenyl-piperazine



To a solution of 1-ethyl-4-phenyl-piperazine (18g, 95mmol) in ethanol (600ml) cooled in an iced bath, was added dropwise bromine (5.1ml, 99mmol). The mixture was stirred at room temperature for 2 hours and then poured into water. The solution was made basic by addition of a solution of NaOH (1N). After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure.

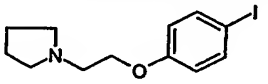
The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 9:1). The title compound was obtained as a solid (21g, 82.4%); [MS APCI] m/z= 270 (M+1).

Intermediate14A: N-(4-bromophenyl)-morpholine



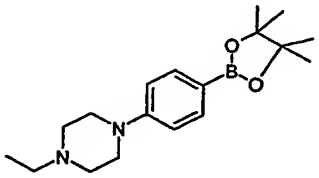
4-Phenyl-morpholine (18g, 110.4mmol) was reacted as described for intermediate 13A to afford, after crystallisation from diisopropyle oxide, the title compound as a white solid (15g, 56.13%); m.p. 126-128°C.

Intermediate 15A: 1-(2-(4-bromo-phenoxy)ethyl]pyrolidine



To a solution of 4-iodo-phenol (6g, 27.3mmol) in acetone (200ml) were added caesium carbonate (22.2g, 68.4mml) and N-(2-chloroethyl)-pyrrolidine hydrochloride (7g, 41 mmol) and the mixture was heated under reflux for 4 hours and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The titled compound was obtained as a red oil (8g, 92.53%); ^1H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.35 (d, 2H), 6.65 (d, 2H), 4.00 (t, 2H), 2.8 (t, 2H), 2.5 (4H, m), 1.7 (4H, m).

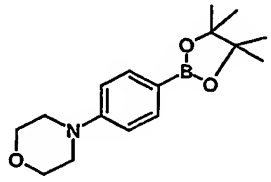
Intermediate 16A: 1-ethyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-piperazine



To a solution of 1-ethyl-4-(4-bromophenyl)-piperazine (3g, 11mmol) in dioxane (100ml) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.8ml, 12mmol), dichlorobis(triphenylphosphine)palladium(II) (0.392g, 0.57mmol), triethylamine (4.65ml, 33mmol) and the mixture was heated under reflux for 12 hours and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by

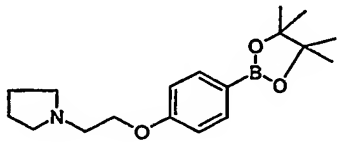
chromatography on silica gel (CH_2Cl_2/MeOH 9:1). The title compound was obtained as a brown oil which crystallised on standing (2g, 55.48%); m.p. 130-134°C.

Intermediate 17A: 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-morpholine



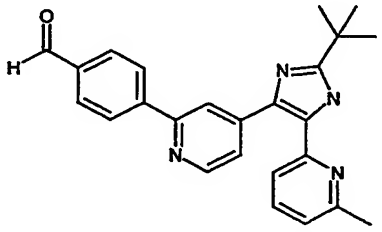
4-(4-Bromophenyl)-morpholine (15g, 62mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.8ml, 68mmol) were reacted as described for intermediate 16A to afford the title compound as a solid (15g, 83.74%); m.p. 114-116°C.

Intermediate 18A: 1-[2-(pyrrolidin-1-yl)-ethoxy]-4-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]-benzene



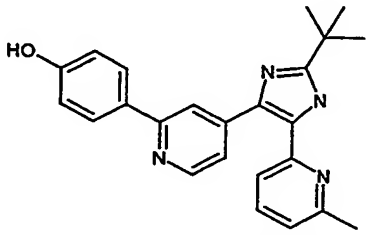
4-(2-(pyrrolidin-1-yl)-ethoxy)-iodobenzene (8g, 25.24mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ml, 27.6mmol) were reacted as described for intermediate 16A to afford the title compound as a pale yellow solid (8g, 99.99%); m.p. 160-164°C.

Intermediate 19A : 4-{4-[2-*tert*-Butyl-5-(6-methyl-pyridin-2-yl)-1*H*-imidazol-4-yl]-pyridin-2-yl}-benzaldhyde



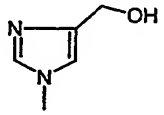
Intermediate 5A (2g, 5.4mmol) and 4-formylphenyl boronic acid (1.13g, 7.56mmol) were reacted as described for example 1A to afford the title compound as a yellow solid (2.37g, quantitative); [MS APCI] m/z 397 (M+1).

Intermediate 20A: 4-{4-[2-*tert*-Butyl-5-(6-methyl-pyridin-2-yl)-1*H*-imidazol-4-yl]-pyridin-2-yl}-phenol



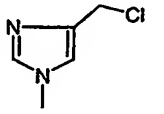
Intermediate 5 (2.5g, 6.7mmol) and 4-hydroxyphenyl boronic acid (1.3g, 9.38mmol) were reacted as described for example 1A to afford the title compound as a brown solid (1.57g, 61%); ^{1}H NMR (350 MHz; $CDCl_3$, ppm) δ: 8.37 (1H, d), 7.70 (1H, s), 7.46 (2H, d), 7.30 (1H, t), 7.20-7.10 (2H, m), 6.83(1H, d), 6.60(1H, d), 3.85-3.23 (4H, brd), 2.27(3H, s), 1.27 (9H, s); [MS APCI] m/z 385 (M+1).

Intermediate 21A : 1-methyl-4-hydroxymethyl-imidazole



To a suspension of 1-methyl-imidazole-4-carboxylic acid (Combi Blocks, 11.4g, 90 mmol) in THF (500ml) at 0°C, was added dropwise $LiAlH_4$ (solution 1M in THF, 117ml, 117 mmol) and the mixture was stirred at room temperature overnight and then at 50°C during 1 hour. Then water (3 ml) was added followed by Na_2SO_4, and the resulting precipitate was filtered off on a celite pad. The filtrate was concentrated under reduced pressure to afford the title compound as a solid (8g, 78.95%); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.25 (s, 1H), 6.70 (s, 1H), 5.25 (m, 1H), 4.40 (s, 2H), 3.45 (s, 3H).

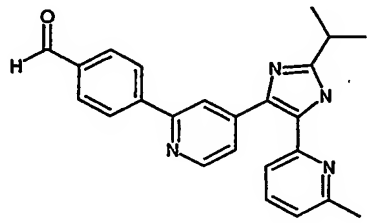
Intermediate 22A : 1-methyl-4-chloromethyl-imidazole



To a solution of intermediate 21A (5g, 44.64 mmol) in CH_2Cl_2 (10 ml) at 0°C was added dropwise thionyl chloride (50 ml) and then the mixture was stirred at room temperature overnight and then under reflux for 3 hours. On cooling the mixture was concentrated under reduced pressure. The residue was treated with diethyl oxide and the resulting precipitate was filtered and dried. The title compound was obtained

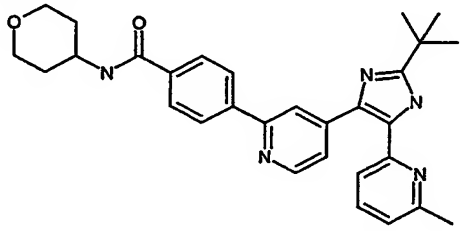
as a brown solid (4g, 53.81%); ^{1}H NMR (300 MHz, DMSO, ppm) δ : 9.25 (s, 1H), 7.8 (s, 1H), 4.95 (s, 2H), 3.9 (s, 3H).

Intermediate 23A: 4-{4-[2-isopropyl-5-(6-methyl-pyridin-2-yl)-1*H*-imidazol-4-yl]-pyridin-2-yl}-benzaldhyde



Intermediate 7A (2.05g, 5.74mmol) and 4-formylphenyl boronic acid (1.2g, 8.04mmol) were reacted as described for example 1A to afford the title compound as a pale yellow solid (1.22g, 56%); ^{1}H NMR (300 MHz; $CDCl_3$, ppm) δ: 9.90 (1H,s), 8.54 (1H, d), 8.02 (2H, d), 7.79 (2H, d), 7.47-7.16 (3H, m), 6.87 (1H, d), 3.12-2.95 (1H, m), 2.39(3H, s), 1.25 (6H, d).

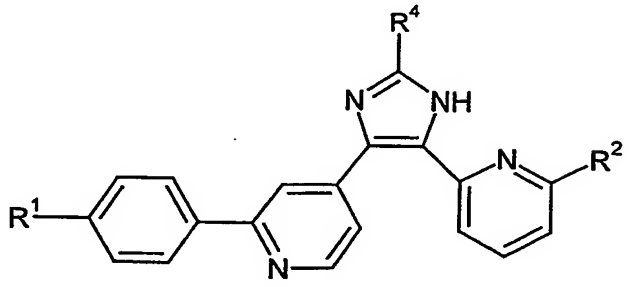
Example 1A : N-(tetrahydropyran-4-yl)-4-(4-{2-*tert*-Butyl-5-[6-methyl-pyridin-2-yl]-1*H*-imidazol-4-yl}-pyridin-2-yl)-benzamide



To a solution of intermediate 5A (0.95g, 2.56mmol) in a mixture of DME (30ml) and water (15ml) were added intermediate 10A (0.93g, 2.81mmol), tetrakis(triphenylphosphine) palladium(0) (0.1g, 0.086mmol) and Na_2CO_3 (solution 2M, 5ml) . The mixture was heated under reflux overnight and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was re-cristallised from EtOAc to afford the title compound as yellow crystals (0.77g, 55.36%); m.p 174°C; TOF MS ES^+ exact mass calculated for $C_{30}H_{33}N_5O_2$ (M+1)+: 496.2712. Found : 496.2662.

The following compounds of formula (IAa), i.e. compounds of general formula (I) where A is imidazole, X is N and R^3 is hydrogen, were prepared using analogous

methods to Example 1A from intermediate 5A, 6A, 7A, 8A or 9A and the appropriate boronic acid starting materials indicated in Table 2.



(IAa)

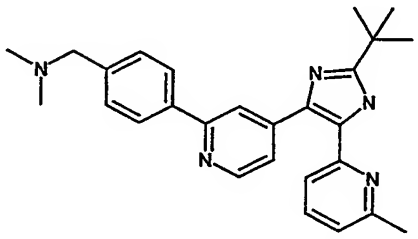
Table 2

Ex	R^1	R^2	R^4	From Intermediates:		Data
2A	N-(tetrahydro-pyran-4-yl)-aminocarbonyl	H	t-Bu	6A	10A	m.p. 182°C; TOF MS ES$^+$ exact mass calculated for $C_{29}H_{31}N_5O_2$ (M+1)+: 482.2556. Found : 482.2577.
3A	methoxy	H	t-Bu	6A	4-methoxy-benzene boronic acid	m.p. 143°C; TOF MS ES$^+$ exact mass calculated for $C_{24}H_{24}N_4O$ (M+1)+: 385.2028. Found: 385.2026.
4A	methane-sulfonyl	Me	t-Bu	5A	4-(methane-sulfonyl)phenyl boronic acid	m.p 144°C; TOF MS ES$^+$ exact mass calculated for $C_{25}H_{26}N_4O_2S$ (M+1)+: 447.1855. Found : 447.1905.
5A	chloro	Me	t-Bu	5A	4-chloro-phenyl boronic acid	m.p. 122°C; TOF MS ES$^+$ exact mass calculated for $C_{24}H_{23}ClN_4$ (M+1)+: 403.1689. Found : 403.1637.
6A	morpholin-4-yl	Me	t-Bu	5A	17A	m.p. 238°C; TOF MS ES$^+$ exact mass calculated for $C_{28}H_{31}N_5O$ (M+1)+: 454.2607. Found : 454.2576.
7A	trifluoro-methoxy	Me	t-Bu	5A	trifluoromethoxy phenyl boronic acid	m.p. 179°C; TOF MS ES$^+$ exact mass calculated for $C_{25}H_{23}F_3N_4O$ (M+1)+:453.1902. Found : 453.1863.
8A	(4-ethyl-piperazin-1-yl)carbonyl	Me	t-Bu	5A	12A	^{1}H NMR (300 MHz; $CDCl_3$) δ: 8.53 (1H, d), 7.93-7.84 (3H, m), 7.40 (1H, d), 7.37-7.27 (3H, m), 7.18 (1H, d), 6.86 (1H, d), 3.85-3.23 (4H, brd), 2.53-2.21(9H, m), 1.31 (9H, s), 0.99 (3H, brs).
9A	morpholin-4yl	H	t-Bu	6A	17A	m.p: 212-214°C; ^{1}H NMR

Ex	R^1	R^2	R^4	From Intermediates:		Data
						(300 MHz; $CDCl_3$) δ: 9.92 (1H, brs), 8.47 (1H, d), 8.38 (1H, d), 7.81 (2H, d), 7.77 (1H, s), 7.36 (2H, d), 7.27(1H, d), 6.95 (1H, dd), 6.80 (2H, d), 3.70 (4H, brt), 3.06 (4H, brt), 1.30 (9H, s).
10A	4-ethyl-piperazin-1-yl	H	t-Bu	6A	12A	m.p: 190-192°C; TOF MS ES^+ exact mass calculated for $C_{29}H_{34}N_6$ (MH^+) 467.2923, found: 467.2880.
11A	2-pyrrolidin-1-yl-ethoxy	H	t-Bu	6A	18A	^1H NMR (300 MHz; $CDCl_3$) δ: 10.02 (1H, brs), 8.63 (1H, d), 8.53 (1H, d), 7.94 (2H, d), 7.91(1H, s), 7.53-7.48 (2H, m), 7.43(1H, d), 7.12-7.06 (1H, m), 6.96 (2H, d), 4.18 (2H, brt), 2.95 (2H, brt), 2.68 (4H, brs),), 1.82 (4H, brs), 1.45 (9H, s).
12A	4-ethyl-piperazin-1-yl	Me	t-Bu	5A	12A	m.p: 210°C; TOF MS ES^+ exact mass calculated for $C_{30}H_{36}N_6$ (MH^+) 481.3080, found: 481.3092.
13A	methane-sulfonyl	H	i-Pr	8A	4-(methane-sulfonyl)phenyl boronic acid	m.p 134°C;TOF MS ES^+ exact mass calculated for $C_{23}H_{22}N_4O_2S$ (M+1)+: 419.1542. Found : 419.1543.
14A	methane-sulfonyl	Me	i-Pr	7A	4-(methane-sulfonyl)phenyl boronic acid	^1H NMR (300 MHz; $CDCl_3$) δ: 8.62 (1H, d), 8.14 (2H, d), 8.09 (1H, s), 7.95 (2H, d), 7.52 (1H, d), 7.45 (1H, t), 7.31 (1H, d), 6.98 (1H, d), 3.16-3.04 (1H, m), 3.02 (3H, s), 2.41 (3H, s), 1.29 (6H, d).
15A	N-(tetrahydro-pyran-4-yl)amino-carbonyl	Me	i-Pr	7A	10A	m.p: 233°C;TOF MS ES^+ exact mass calculated for $C_{29}H_{31}N_5O_2$ (M+1)+: 482.2556. Found : 482.2509.
16A	morpholin-4-yl	Me	i-Pr	7A	17A	^1H NMR (300 MHz; $CDCl_3$) δ: 10.52 (1H, brs), 8.58 (1H, d), 7.94 (2H, d), 7.90 (1H, s), 7.45-7.30(3H, m), 7.00-6.87 (3H, m), 6.80 (2H, d), 3.83 (4H, brt),3.20 (4H, brt), 3.17-3.06 (1H, m), 2.47 (3H, s), 1.35 (6H, d).
17A	morpholin-4-yl	Me	Me	9A	17A	^1H NMR (300 MHz; $CDCl_3$) δ: 8.65 (1H, d), 8.03 (1H, s), 7.97 (2H, d), 7.55-

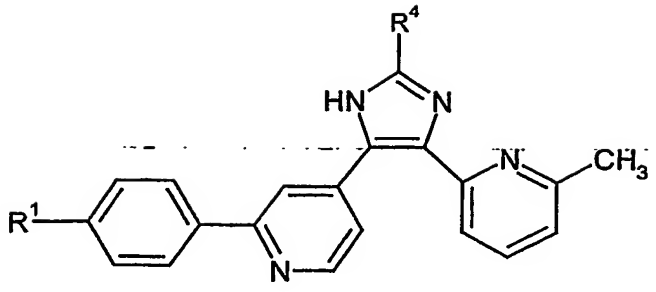
Ex	R^1	R^2	R^4	From Intermediates:		Data
						7.40(3H, m), 7.04(1H, d), 6.97 (2H, d), 3.89 (4H, brt), 3.26 (4H, brt), 2.59 (3H, s), 2.56 (3H, s), NH imidazole not seen.
18A	morpholin-4-ylcarbonyl	Me	Me	9A	11A	^{1}H NMR (300 MHz; $CDCl_3$) δ: 8.72 (1H, d), 8.14 (1H, s), 8.09 (2H, d), 7.63-7.41(5H, m), 7.08(1H, d), 3.94-3.62 (8H, m), 2.62 (3H, s), 2.60 (3H, s), NH imidazole not seen.
19A	morpholin-4-ylcarbonyl	Me	t-Bu	5A	11A	m.p. 180°C; TOF MS ES$^+$ exact mass calculated for $C_{29}H_{31}N_5O_2$: 482.2556 (MH^+). Found : 482.2517 (MH^+).

Example 20A : (4-{4-[2-*tert*-Butyl-5-(6-methyl-pyridin-2-yl)-1*H*-imidazol-4-yl]-pyridin-2-yl}-benzyl)-dimethyl-amine



To a solution of intermediate 19A (0.8g, 2.02mmol) in CH_2Cl_2 (50ml) were added dimethylamine (solution2M in MeOH, 1.1ml, 2.22mmol) and sodium triacetoxyborohydride (0.856g, 4.04mmol). The mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 . The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The title compound was obtained, after chromatography on silicagel (CH_2Cl_2/MeOH 98:2 then 85:15) and recrystallisation from EtOAc, as a white solid (0.109g, 12.6%); m.p. 187°C; TOF MS ES$^+$ exact mass calculated for $C_{27}H_{31}N_5$ (M+1)+:426.2657. Found : 426.2680.

The following compounds of formula (IAb), i.e. compounds of general formula (I) where A is imidazole, X is N, R^1 is $-CH_2NR^5R^6$, R^2 is methyl and R^3 is hydrogen, were prepared using analogous methods to Example 20A from intermediate 5A or 7A and the boronic acid starting materials indicated in Table 3

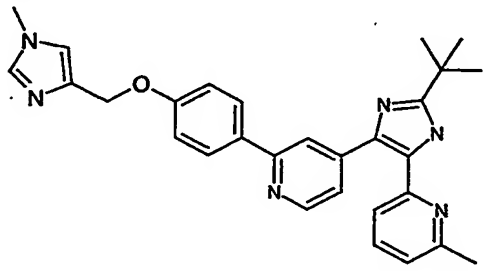


(IAb)

Table 3

Ex	R^1	R^4	From intermediates:		Data
21A	morpholin-4-ylmethyl	t-Bu	19A	morpholine	^{1}H NMR (300 MHz; $CDCl_3$) δ: 8.77 (1H, d), 8.13 (1H, s), 8.05 (2H, d), 7.65-7.41(5H, m), 7.09(1H, d), 3.88-3.78 (4H, m), 3.69-3.62 (2H, m), 2.64 (3H, s), 2.60-2.54 (4H, m), 1.56 (9H, s), NH imidazole not seen; TOF MS ES$^+$ exact mass calculated for $C_{29}H_{33}N_5O$: 468.2763 (MH^+. Found : 468.2764 (MH^+).
22A	pyrrolidin-1-ylmethyl	t-Bu	19A	pyrrolidine	M.p: 148°C; TOF MS ES$^+$ exact mass calculated for $C_{29}H_{33}N_5$: 452.2814 (MH^+). Found : 452.2814 (MH^+).
23A	morpholin-4-ylmethyl	i-Pr	23A	morpholine	m.p:141°C; TOF MS ES$^+$ exact mass calculated for $C_{28}H_{31}N_5O$: 454.2607 (MH^+). Found : 454.2574 (MH^+).
24A	Dimethylamino methyl	i-Pr	23A	dimethylamine	m.p. 135°C; TOF MS ES$^+$ exact mass calculated for $C_{26}H_{29}N_5$: 412.2501 (MH^+) Found : 412.2523 (MH^+).

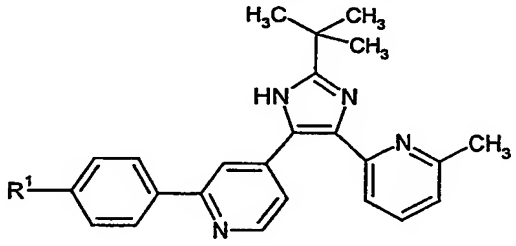
Example 25A : 4-(2-*tert*-Butyl-5-{6-methyl}-pyridin-2-yl-1*H*-imidazol-4-yl)-2-[4-(1-methyl-1*H*-imidazol-4-ylmethoxy)-phenyl]-pyridine



To a solution of intermediate 20A (0.49g, 1.27mmol) in DMF (20ml) was added portionwise sodium hydride (60% in mineral oil, 0.152g, 3.81mmol) and the mixture was stirred at room temperature for 10 minutes. Intermediate 22A (0.3g, 1.8mmol)

was then added and the mixture was stirred for 18 hours at room temperature and then poured into water. After extraction with AcOEt, the organic phase was washed with a solution of NaOH1N and water, dried over Na_2SO_4 and concentrated under reduced pressure. After precipitation with pentane, the title compound was obtained as an off-white solid (0.305g, 50%), gummy at 128°C; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 8.51 (1H, d), 7.87 (1H, s), 7.82 (2H, d), 7.40 (1H, d), 7.40-7.28 (3H, m), 7.22 (1H, d), 6.96 (1H, d), 6.89 (1H, d), 6.85 (1H, s), 4.97 (2H, s), 3.56 (3H, s), 2.36 (3H, s), 1.32 (9H, s); TOF MS ES$^+$ exact mass calculated for $C_{29}H_{30}N_6O$ (MH^+) 479.2559 , found 479.2549.

The following compounds of formula (IAc), i.e. compounds of general formula I where A is imidazole, X is N, R^1 is $-O(CH_2)_nNR^5R^6$, R^2 is methyl, R^3 is hydrogen and R^4 is tert-butyl, were prepared using analogous methods to Example 25A from intermediate 5A and the boronic acid starting materials indicated in Table 4.

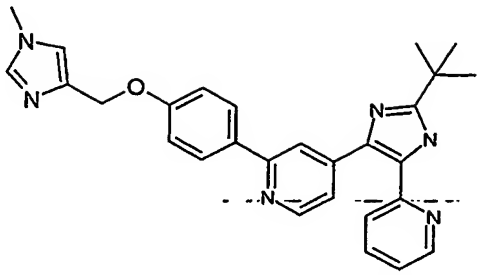


(IAb)

Table 4

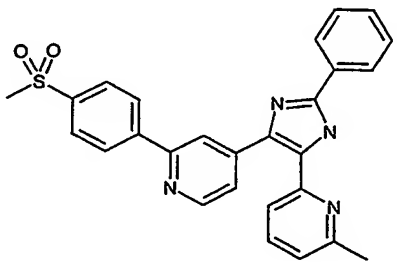
Ex	R^1	From intermediate:		Data
26A	$H_2NC(O)CH_2O$-	20A	2-bromoacetamide	M.p: 210°C; TOF MS ES$^+$ exact mass calculated for $C_{26}H_{27}N_5O_2$ (MH^+)442.2243, found: 442.2221.
27A	2-pyrrolidin-1-yl-ethoxy	20A	1-(2-chloroethyl)-pyrrolidine hydrochloride	M.p: 168°C; TOF MS ES$^+$ exact mass calculated for $C_{30}H_{35}N_5O$ (MH^+)482.2920, found/ 482.2931

Example 28A : 4-(2-*tert*-Butyl-5-pyridin-2-yl-1*H*-imidazol-4-yl)-2-[4-(1-methyl-1*H*-imidazol-4-ylmethoxy)-phenyl]-pyridine



To a solution of example 3A (0.26g , 0.67mmol) in CH_2Cl_2 (40ml) was added boron tribromide (2.1ml, 2.1mmol, 3.2eq, solution 1M in CH_2Cl_2). The mixture was stirred at room temperature overnight. The reaction mixture was evaporated and neutralised with NaOH 1N, the resulting mixture was warmed up to 60°C and stirred for 1hour. After cooling at room temperature, the mixture was extracted with CH_2Cl_2 . The aqueous phase was acidified with HCl 1N and extracted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to give 4-(4-{2-*tert*-Butyl-5-pyridin-2-yl-1*H*-imidazol-4-yl}-pyridin-2-yl]-phenol which was used without purification in the next step. To a solution of 4-(4-{2-*tert*-Butyl-5-pyridin-2-yl-1*H*-imidazol-4-yl}-pyridin-2-yl]-phenol (0.14g, 0.37mmol) in acetone K_2CO_3 (0.156g, 1.1mmol) and intermediate 25 (0.094g, 0.56mmol) were heated at reflux for 2 days. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was poured into water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silicagel (toluene/ isopropylamine 90:10) to afford the tittle compound as a yellow solid (0.04g, 23.3%); m.p. 156°C; TOF MS ES^+ exact mass calculated for $C_{28}H_{28}N_6O$ (MH^+) 465.2403, found: 465.2395.

Example 29A: 4-{2-Phenyl-5-[6-methyl]-pyridin-2-yl-1*H*-imidazol-4-yl}-2-(4-methanesulfonyl-phenyl)-pyridine



Intermediate 3A (6.5g, 20.3mmol) and benzaldehyde (4.3ml, 40.6mmol) were reacted as described for intermediate 5A to afford 2-phenyl-4-(pyridin-2-yl)-5-(2-

bromo-pyridin-4-yl)-imidazole (4.5g) which was used in the next step without purification. 2-Phenyl-4-(pyridin-2-yl)-5-(2-bromo-pyridin-4-yl)-imidazole (0.6g, 1.53mmol) and 4-(methanesulfonyl)phenyl boronic acid (0.338g, 1.69mmol) were reacted as described for example 1A to afford the title compound as a yellow powder (0.14g, 19.63%); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 8.67 (1H, d), 8.13-8.12 (2H, m), 7.96 (2H, d), 7.92 (1H, s), 7.68-7.26(8H, m), 7.02 (1H, d), 3.02 (3H, s), 2.54 (3H, s). TOF MS ES$^+$ exact mass calculated for $C_{27}H_{22}N_4O_2S$ (M+1)+: 467.1542. Found : 467.1513.

Experimental for imidazo[1,2-*a*]pyridines (B)

Intermediate 1B: 3-Chloro-4-fluoro-benzoic acid ethyl ester

To a solution of 3-chloro-4-fluoro-benzoic acid (ACROS?, 11.75 g, 67.3 mmol) in EtOH was added APTS (1.2 g). The resulting mixture was heated under reflux for 2 days and then poured into water. The aquous phase was basified with a solution of 1N NaOH, extracted with DCM and the combined organic phases were dried over Na_2SO_4. Concentration under reduced pressure gave the title compound as an oil (13.08g, 96%); [APCI MS] m/z 203 MH$^+$.

Intermediate 2B: 3,4-Difluoro-benzoic acid ethyl ester

3,4-Difluoro-benzoic acid (ACROS, 11 g, 69.57 mmol) was reacted as described for intermediate 1B to afford the title compound as an oil (11.78g, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.84 (m, 2H), 7.22 (m, 1H), 4.37 (q, 2H), 1.38 (t, 3H).

Intermediate 3B: 6-Methyl-pyridine-2-carboxylic acid ethyl ester

6-Methyl-pyridine-2-carboxylic acid (INTERCHIM, 25g, 182.3 mmol) was reacted as described for intermediate 1B to afford the title compound as an oil (22.9g, 76.13%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.95 (d, 1H), 7.75 (t, 1H), 7.35 (d, 1H), 4.5 (q, 2H), 2.7 (s, 3H), 1.45 (t, 3H).

Intermediate 4B: 6-Fluoro-pyridine-2-carboxylic acid

To a solution of 2-fluoro-6-methyl-pyridine (2.5g , 22.5 mmol) in water (170 ml) was added portionwise $KMnO_4$ (2g, 12.65 mmol) and the mixture was heated to reflux. Further $KMnO_4$ (8g, 50.63 mmol) was added portionwise and the mixture was heated under reflux for 3 hours and then cooled. The precipitate was filtered off, the filtrate acidified with hydrochloric acid and then concentrated under reduced pressure. The residue was triturated with hot EtOH, the solid was filtered off and the filtrate was

concentrated to dryness under reduced pressure. The title compound was obtained as a white solid (1.7g, 53%); m.p. 137°C.

Intermediate 5B: 6-Fluoro-pyridine-2-carboxylic acid isopropyl ester

6-Fluoro-pyridine-2-carboxylic acid (1g, 7.09 mmol) was added portion-wise to thionyl chloride (3 ml) and the mixture was heated under reflux for 3 hours and then concentrated under reduced pressure. Isopropanol (3 ml) was added to the residue and the mixture was stirred at room temperature for 5 minutes and then concentrated under reduced pressure. The residue was treated with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The title compound was obtained as an oil (1.2g, 93%); [APCI MS] m/z: 184 MH^+.

Intermediate 6B: 1-Methyl-4-hydroxymethyl-imidazole

To a suspension of 1-methyl-imidazole-4-carboxylic acid (Combi Blocks, 11.4g, 90 mmol) in THF (500ml) at 0°C, was added dropwise a solution of lithium aluminium hydride (1M in THF, 117ml, 117 mmol) and the mixture was stirred at room temperature overnight and then at 50°C for 1 hour. Water (3 ml) was added followed by Na_2SO_4 and the mixture was filtered through celite™. The filtrate was concentrated under reduced pressure to afford the title compound as a solid (8g, 78.95%); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 7.25 (s, 1H), 6.7 (s, 1H), 5.25 (m, 1H), 4.4 (s, 2H), 3.45 (s, 3H).

Intermediate 7B: 1-Methyl-4-chloromethyl-imidazole

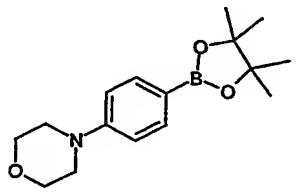
To a solution of intermediate 6B (5g, 44.64 mmol) in DCM (10 ml) at 0°C was added dropwise thionyl chloride (50 ml) and the mixture was stirred at room temperature overnight and then at reflux for 3 hours. The mixture was concentrated under reduced pressure and the residue taken up in diethyl ether to give a precipitate. The precipitate was filtered and dried to give the title compound (4g, 53.81%); ^1H NMR (300 MHz, DMSO) δ ppm: 9.25 (s, 1H), 7.8 (s, 1H), 4.95 (s, 2H), 3.9 (s, 3H).

Intermediate 8B: 4-(Morpholin-4-yl)-bromobenzene

To an ice-cooled solution of 4-phenyl-morpholine (18g, 110.4 mmol) in ethanol (400ml), was added dropwise bromine (5.95 ml, 115.9 mmol). After addition the mixture was warmed to room temperature and stirred for 2 hours. The mixture was poured into water and the solution was basified with 1N sodium hydroxyde solution.

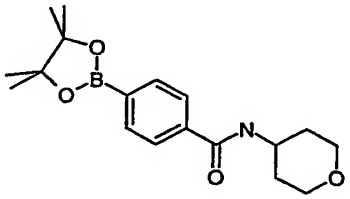
The resulting precipitate was filtered, washed with water and dried. Recrystallisation from diisopropyl ether gave the title compound as white crystals (15g, 56.13%); m.p. 126-128°C.

Intermediate 9B: N-[4-(4,4,5,5-Tetramethyl-[1,3,2]-dioxaborolan-2-yl)-phenyl]-morpholine



To a solution of intermediate 8B (20g, 82.64 mmol) in dioxane (200 ml) was added 4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (13.2 ml, 99.17 mmol) , dichloro bis(triphenylphosphine) palladium (II) (3g, 4.13 mmol) and triethylamine (34.5 ml, 247.93 mmol) and the mixture was heated under reflux for 4 hours. The reaction mixture was cooled, poured into water and extracted with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with DCM to give the title compound was obtained as an orange oil which crystallised (19.98 g, 83.94%); [APCI MS] m/z 289.07 MH^+.

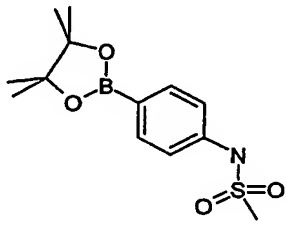
Intermediate 10B: 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-*N*-(tetrahydro-pyran-4-yl)-benzamide



4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (70.16g, 0.28 mol) was treated with thionyl chloride (2 vol) and the reaction mixture was stirred at reflux for 2 hours. The mixture was cooled and evaporated to give a residue. The residue was dissolved in toluene and the mixture was poured into a solution of tetrahydro-pyran-4-ylamine (34.34g, 0.339) and triethylamine (79 mL, 0.57 mol) in DCM at 10°C. The mixture was warmed to room temperature and stirred for 2 days. Addition of water (490 ml) gave a precipitate which was filtered off and washed with AcOEt. Purification by flash chromatography eluting with DCM/MeOH (95/05) gave the title

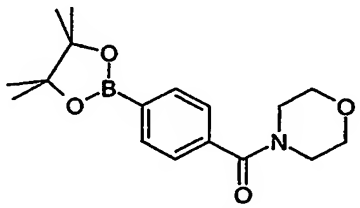
compound as a solid (17.02g, 18%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.85 (d, 2H), 7.72 (d, 2H), 5.98 (m, 1H), 4.20 (s, 1H), 3.99 (m, 2H), 3.35 (t, 2H), 2.01 (d, 2H), 1.57 (m, 2H), 1.35 (s, 12H).

Intermediate 11B: N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide



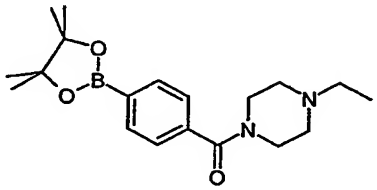
To a solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-aniline (Aldrich, 5g, 22.8 mmol) in DCM (20ml) was added $NaHCO_3$ (2.3g, 27.4 mmol) and methanesulfonyl chloride (13.2 mL, 171 mmol) and the reaction mixture was stirred at room temperature for 6 days. Water was added and the mixture was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallisation from diethyl ether to give the title compound as a white powder (2.52g, 37%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.78 (d, 2H), 7.18 (d, 2H), 6.69 (m, 1H), 3.02 (s, 3H), 1.33 (s, 12H).

Intermediate 12B: N-[(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl)carbonyl]-morpholine



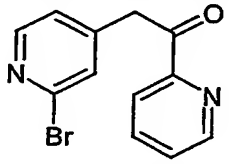
To a solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (5g, 20.15 mmol) in DCM/DMF (50ml/5ml) was added morpholine (2.1ml, 24.2mmol), HOBT (3.3g, 24.2mmol), EDCI (4.65g, 24.2mmol) and triethylamine (4.2ml, 30.2mmol) and the reaction mixture was stirred at room temperature for 3 days. Water was added and the product was extracted with DCM. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a reside. Trituration of the residue with diisopropyl ether gave the title product as a white solid (4.21g, 66%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.8 (d, 2H), 7.4 (d, 2H), 3.7 (m, 4H), 3.55 (m, 2H), 3.35 (m, 2H), 1.3 (s, 12H).

Intermediate 13B: 1-Ethyl-4-[(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl)carbonyl]-piperazine



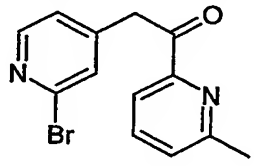
4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (8.24g, 33.22 mmol) and N-ethylpiperazine (5.1ml, 39.87mmol) were reacted as described for intermediate 12B to give, after chromatography on silicagel (CH_2Cl_2/MeOH, 95/5), the title compound (9.64g, 84%); [APCI MS] m/z 345 MH^+.

Intermediate 14B: 2-[2-Bromo-pyridin-4-yl]-1-pyridin-2-yl-ethanone



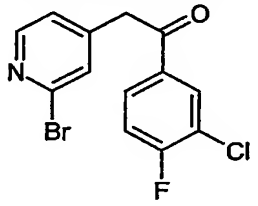
To a solution of 2-bromo-4-methyl-pyridine (ALDRICH, 27 g, 157 mmol) in dry THF (270 ml) was added ethyl picolinate (28.5 g, 188.7 mmol). The resulting mixture was cooled to -78°C under argon and a solution of sodium bis-(trimethylsilyl)amide (1M in THF, 345 ml, 345 mmol) was added dropwise at -78°C. The reaction mixture was allowed to reach room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue triturated with diethyl ether. The solid was filtered and washed with diethyl ether. The solid was then taken up in saturated NH_4Cl solution and the aqueous phase extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to give an orange powder which was washed with pentane to give the title compound as a yellow solid (33.97 g); m.p. 111.2°C.

Intermediate 15B: 2-[2-Bromo-pyridin-4-yl]-1-(6-methyl-pyridin-2-yl)-ethanone



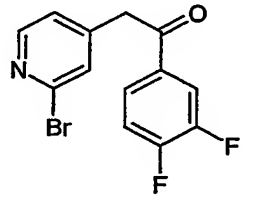
A solution of sodium bis-(trimethylsilyl)amide (2M in THF, 32 ml, 64 mmol) was added dropwise at –30°C to a solution of 2-bromo-4-methyl-pyridine (5 g, 29mmol) in dry THF (70 ml). The mixture was stirred at –30°C for 1 hour and then 6-methylpicolinic acid methyl ester (4.82 g, 32.3mmol, 1.1eq) was added. The reaction mixture was stirred at room temperature overnight. Diethyl ether was added and the resulting solid was filtered and washed with diethyl ether. The solid was taken up in saturated NH_4Cl solution and the aqueous phase was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The resulting orange powder was washed with pentane to give the title compound as a yellow solid (5.84g, 70%); MS (APCI) : 292 (MH+).

Intermediate 16B: 2-(2-Bromo-pyridin-4-yl)-1-(3-chloro-4-fluoro-phenyl)-ethanone



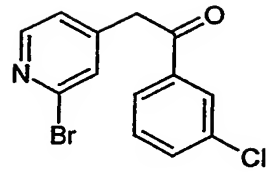
2-Bromo-4-methyl-pyridine (9.2g , 53.5 mmol) and 3-chloro-4-fluoro-benzoic acid ethyl ester (13 g, 64.2 mmol) were reacted as described for intermediate 14B to afford the title compound as an orange solid (17.16 g, 98%); [APCI MS] m/z: 330 (MH+).

Intermediate 17B: 2-(2-Bromo-pyridin-4-yl)-1-(3,4-difluoro-phenyl)-ethanone



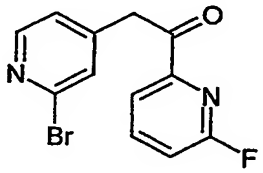
2-Bromo-4-methyl-pyridine (9.056g , 52.64 mmol) and 3,4-difluoro-benzoic acid ethyl ester (11.75 g, 63.17 mmol) were reacted as described for intermediate 14B to afford the title compound as an ocre solid (14.54 g, 88.5%); [APCI MS] m/z: 314 (MH+).

Intermediate 18B : 2-(2-Bromo-pyridin-4-yl)-1-(3-chloro-phenyl)-ethanone



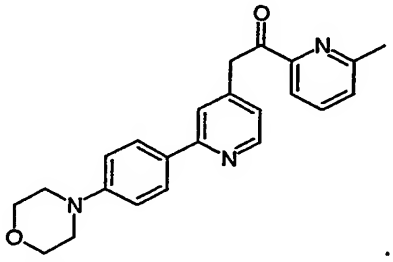
2-Bromo-4-methyl-pyridine (7.75g , 45.1 mmol) and methyl-3-chlorobenzoate (10 g, 58.6 mmol) were reacted as described for intermediate 14B to afford the title compound as an orange powder (13.02 g, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.34 (d, 1H), 7.95 (m, 1H), 7.84 (d, 1H), 7.59 (d, 1H), 7.46 (d, 1H), 7.41 (d, 1H), 7.13 (d, 1H), 4.24 (s, 2H).

Intermediate 19B: 2-(2-Bromo-pyridin-4-yl)-1-(6-fluoro-pyridin-2-yl)-ethanone



To a solution of 2-bromo-4-methyl-pyridine (2.58g, 15 mmol) in anhydrous THF (50 ml) at –30°C, was added dropwise NaHMDS (solution 2M in THF, 15ml, 30 mmol) and the mixture was stirred at –30°C for 2 hours. A solution of intermediate 5 (2.74g, 15 mmol) in THF (50 ml) was added dropwise and the mixture was stirred at –30°C for 1 hour. The mixture was allowed to reach room temperature and poured into water. The mixture was extracted with AcOEt, the combined organic phases were dried over Na_2SO_4 and the mixture was concentrated under reduced pressure. The concentrate was purified by chromatography on silica gel (DCM/MeOH, 99/1) to give the title compound as a yellow solid (1.6g, 36%); [APCI MS] m/z: 295 (MH+).

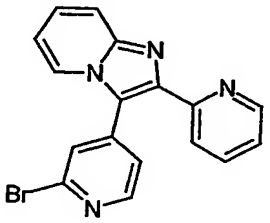
Intermediate 20B: 2-(2-(4-(Morpholin-4-yl)phenyl)-pyridin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone



To a solution of intermediate 15B (3g, 10.3 mmol) in DME (100 mL) was added tetrakis triphenylphosphine palladium(0) (1.2g , 10%mol), intermediate 7B (3.86g, 13.4 mmol) and Na_2CO_3 (2M, 10.3 ml) and the mixture was heated under reflux for

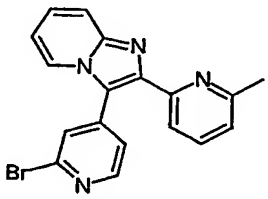
18 hours. The cooled mixture was poured into water and extracted with DCM. The organic phase was washed with water, dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave a crude oil which was purified by chromatography on silica gel (DCM/MeOH, 97/3) to give the title compound (3.77g, 98%); [APCI MS] m/z: 374.13 (MH+).

Intermediate 21B: 3-(2-Bromo-pyridin-4-yl)-2-(pyridin-2-yl)-imidazo[1,2-a]pyridine



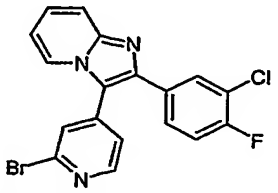
To a solution of intermediate 14B (5g, 18.05mmol) in DCM (30 ml) was added bromine-polymer-supported (Aldrich, 11.28g, 18.05 mmol) and the suspension was stirred at room temperature during 5 hours. The suspension was filtered washing through ethanol. The filtrate and washings were added to 2-aminopyridine (ALDRICH, 3.4 g , 36.06 mmol) and the mixture heated under reflux for 18 hours. On cooling the mixture was concentrated and the residue was extracted between water and DCM. The combined organic phases was dried over Na_2SO_4 and evaporated under reduced pressure to give a crude solid which was precipitated from diisopropyl ether to afford the title compound (3.053g; 48%); m.p. 227°C.

Intermediate 22B: 3-(2-Bromo-pyridin-4-yl)-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



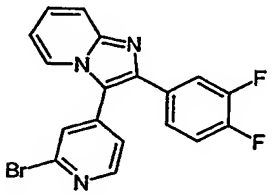
Intermediate 15B (5g, 17.18mmol) and 2-aminopyridine (3.23g, 34.32mmol) were coupled and treated as described for intermediate 21B to afford the title compound as a brown powder (3.621g, 58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.47 (d, 1H); 8.12 (d, 1H); 7.8 (m, 2H); 7.7 (d, 1H); 7.6 (t,1H); 7.47 (d, 1H); 7.29 (t, 1H); 7.05 (d, 1H); 6.85 (t,1H) ; 2.39 (s, 3H).

Intermediate 23B: 3-(2-Bromo-pyridin-4-yl)-2-(3-chloro-4-fluoro-phenyl)-imidazo[1,2-a]pyridine



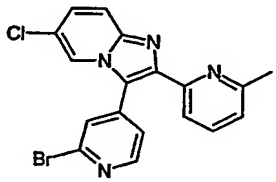
Intermediate 16B (5g, 15.22 mmol) and 2-amino-pyridine (2.86g , 30.44mmol) were coupled and treated as described for intermediate 21B to afford the title compound (3g, 49%); [APCI MS] m/z 404 (MH+).

Intermediate 24B: 3-(2-Bromo-pyridin-4-yl)-2-(3,4-difluoro-phenyl)-imidazo[1,2-a]pyridine



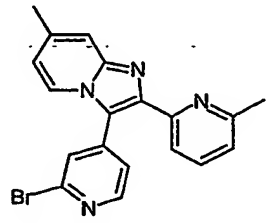
Intermediate 17B (5g, 16 mmol) and 2-aminopyridine (3g, 32 mmol) were coupled and treated as described for intermediate 21B to afford, after crystallisation from diisopropyl ether, the title compound as a brown powder (2.95g, 88%); [APCI MS] m/z 386 (MH+).

Intermediate 25B: 3-(2-Bromo-pyridin-4-yl)-6-chloro-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



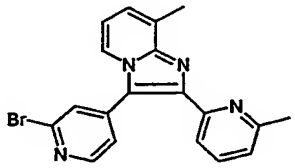
Intermediate 15B (2g, 6.87 mmol) and 2-amino-5-chloropyridine (1.77g, 13.75 mmol) were coupled and treated as described for intermediate 21B to afford the title compound as a brown powder (1.152g, 42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.50 (d, 1H), 8.09 (d, 1H), 7.82 (s, 2H), 7.65 (t, 2H), 7.45 (d, 1H), 7.27 (d, 1H), 7.08 (d, 1H), 2.39 (s, 3H).

Intermediate 26B: 3-(2-Bromo-pyridin-4-yl)-7-methyl-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



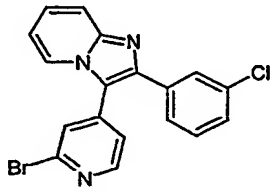
Intermediate 15B (2.53g, 6.87 mmol) and 2-amino-4-picoline (1.49g, 13.75 mmol) were reacted and treated as described for intermediate 21B to afford the title compound as a brown solid (1.43g, 55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.43 (d, 1H), 8.00 (d, 1H), 7.82 (s, 1H), 7.78 (d, 1H), 7.60 (t, 1H), 7.44 (m, 2H), 7.05 (d, 1H), 6.70 (d, 1H), 2.43 (s, 3H), 2.40 (s, 3H).

Intermediate 27B: 3-(2-Bromo-pyridin-4-yl)-8-methyl-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



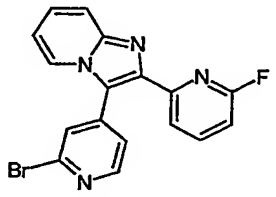
Intermediate 15B (5g, 17.24 mmol) and 2-amino-3-picoline (3.73g, 34.5 mmol) were coupled and treated as described for intermediate 21B to afford the title compound as a brown solid (4.08g, 62%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.55 (d, 1H), 8 (d, 1H), 7.85 (d, 1H), 7.8 (s, 1H), 7.65 (t, 1H), 7.45 (d, 1H), 7.1 (m, 2H), 6.8 (t, 1H), 2.7 (s, 3H), 2.4 (s, 3H).

Intermediate 28B : 3-(2-Bromo-pyridin-4-yl)-2-(3-chloro-phenyl)-imidazo[1,2-a]pyridine



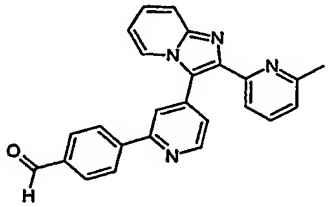
Intermediate 18B (13g, 42.1 mmol) and 2-amino-pyridine (7.9g, 2eq, 84 mmol) were coupled and treated as described for intermediate 21B to afford the title compound as a yellow solid (8.45g, 52%); [APCI MS] m/z 384 (MH+).

Intermediate 29B: 3-(2-Bromo-pyridin-4-yl)-2-(6-fluoro-pyridin-2-yl)-imidazo[1,2-a]pyridine



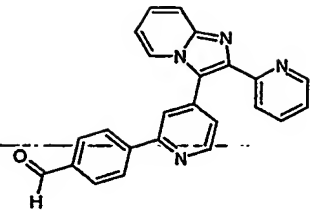
Intermediate 19B (0.65g, 2.1 mmol) and 2-aminopyridine (0.42g, 4.4 mmol) were coupled and treated as described for intermediate 21B to afford, after trituration with diisopropyl ether, the title compound as a cream solid (199mg, 25%); [APCI MS] m/z 369 (MH+).

Intermediate 30B: 3-(2-(4-Formyl-phenyl)-pyridin-4-yl)-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



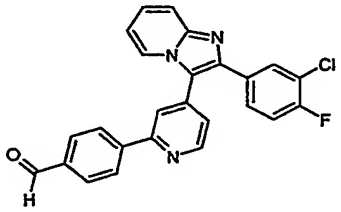
A solution of intermediate 22B (500mg, 1.37 mmol) in DME (50 ml) was treated with tetrakis triphenylphosphine palladium(0) (158 mg, 10%mol) and stirred at room temperature for 30 min. Aqueous Na_2CO_3 (2M, 4.2 ml) was added to the reaction mixture, followed by 4-formyl-phenyl boronic acid (Lancaster, 267mg, 1.78 mmol) and the mixture was heated under reflux overnight. The cooled mixture was poured into ice and extracted with DCM. The layers were separated and the organic phase was washed with water, dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave a crude oil which was purified by chromatography on silica gel (DCM/MeOH 95:5) to give the title compound (310 mg, 58%); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 10.08 (s, 1H) ; 8.86 (d, 1H); 8.10-8.20 (m, 4H); 7.98 (d, 1H); 7.83 (d, 1H); 7.75 (d,1H); 7.61 (t, 1H); 7.51 (m, 1H); 7.30 (t, 1H); 7.04 (d, 1H) ; 6.85(t,1H) ; 2.31 (s, 3H).

Intermediate 31B: 3-(2-(4-Formyl-phenyl)-pyridin-4-yl)-2-pyridin-2-yl-imidazo[1,2-a]pyridine



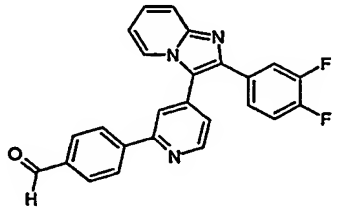
Intermediate 21B (1.2g, 3.4mmol) and 4-formyl-phenyl boronic acid (LANCASTER, 612mg, 4.1mmol) were coupled and treated as described for intermediate 30 to afford after crystallisation from acetonitrile, the compound as a cream powder (1.1g, 86%); m.p. 216-218°C; [APCI MS] m/z 377 (MH+).

Intermediate 32B: 3-(2-(4-Formyl-phenyl)-pyridin-4-yl)-2-(3-chloro-4-fluoro-phenyl)-imidazo[1,2-a]pyridine



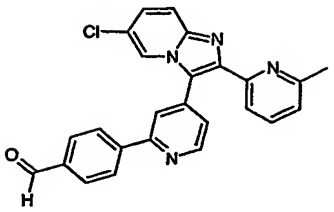
Intermediate 23B (1g, 2.48 mmol) and 4-formyl-phenyl boronic acid (LANCASTER, 484mg, 3.22 mmol) were coupled and treated as described for intermediate 30B to afford, after purification by chromatography on silica gel (DCM/MeOH 98:2), the title compound as a yellow solid (380 mg, 36%); [APCI MS] m/z 428 (MH+).

Intermediate 33B: 3-(2-(4-Formyl-phenyl)-pyridin-4-yl)-2-(3,4-difluoro-phenyl)-imidazo[1,2-a]pyridine



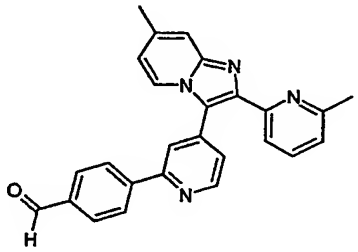
Intermediate 24B (1g, 2.6 mmol) and 4-formyl-phenyl boronic acid (LANCASTER, 506mg, 3.37 mmol) were coupled and treated as described for intermediate 30B to afford the title compound as a solid (600 mg, 56%); [APCI MS] m/z 412 (MH+).

Intermediate 34B: 6-Chloro-3-(2-(4-formyl-phenyl)-pyridin-4-yl)-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



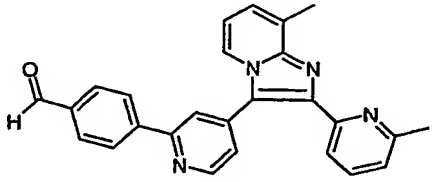
Intermediate 25B (1.15g, 2.88 mmol) and 4-formyl-phenyl boronic acid (LANCASTER, 563mg, 3.75 mmol) were reacted and treated as described for intermediate 30B to afford, after purification by chromatography on silica gel (DCM/MeOH 90:10), the title compound (1.15g, 93%); [APCI MS] m/z 425 (MH+).

Intermediate 35B: 7-Methyl-3-(2-(4-formyl-phenyl)-pyridin-4-yl)-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



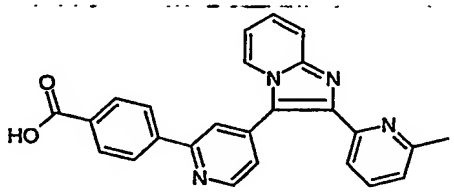
Intermediate 26B (1.43g, 3.78 mmol) and 4-formylbenzene boronic acid (LANCASTER, 738mg, 4.92 mmol) were coupled and treated as described for intermediate 30B to afford, after purification by flash chromatography on silica gel (DCM/MeOH 95:5), the title compound as an orange foam (270mg, 18%); [APCI MS] m/z 405 (MH+).

Intermediate 36B: 8-Methyl-3-(2-(4-formyl-phenyl)-pyridin-4-yl)-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



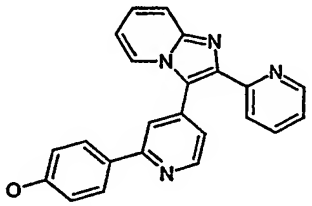
Intermediate 27B (1.5g, 3.97 mmol) and 4-formylbenzene boronic acid (LANCASTER, 0.773g, 5.16 mmol) were coupled and treated as described for intermediate 30B to afford the title compound as a cream powder (1.39g, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm:10.1 (s, 1H), 8.9 (d, 1H), 8.2 (d, 2H), 8.15 (s, 1H), 8.1 (d, 1H), 8 (d, 2H), 7.85 (d, 1H), 7.6 (m, 2H), 7.1 (m, 2H), 6.8 (t, 1H), 2.8 (s, 3H), 2.4 (s, 3H).

Intermediate 37B : 3-[2-[4-(Carboxy)-phenyl]-pyridin-4-yl}-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



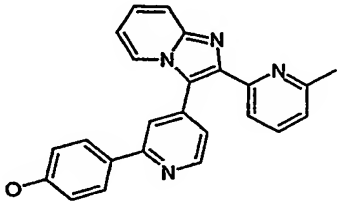
Intermediate 22B (2g, 5.49 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-benzoic acid (ALDRICH, 2.04g, 8.24 mmol) were coupled and treated as described for intermediate 30 to afford, after trituration with DCM/diisopropyl ether, the title compound (1.4g, 62.76%); [APCI MS] m/z 407 (MH+).

Intermediate 38B: 3-(2-(4-Hydroxy-phenyl)-pyridin-4-yl)-2-(pyridin-2-yl)-imidazo[1,2-a]pyridine



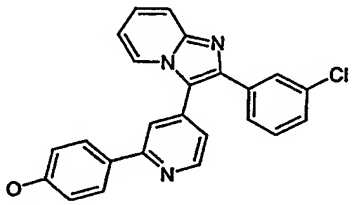
Intermediate 21B (1.85g, 5.27 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-phenol (Aldrich, 1.5 g, 6.85 mmol) were coupled and treated as described for intermediate 30B to afford, after purification by flash chromatography on silica gel (DCM/MeOH, 98/2 then 95:5 then 93/7), the title compound 1.4 g, 73%); [APCI MS] m/z = 365 (MH+).

Intermediate 39B: 3-(2-(4-Hydroxy-phenyl)-pyridin-4-yl)-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



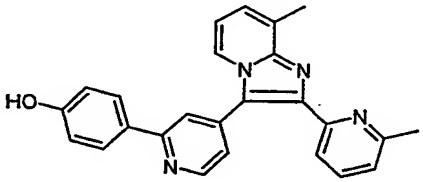
Intermediate 22B (1g, 2.74 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-phenol (Aldrich, 786mg, 3.57 mmol) were coupled and treated as described for intermediate 30B to afford, after purification by chromatography on silica gel (DCM/MeOH 90:10), the title compound (470 mg, 45%); [APCI MS] m/z 379 MH^+.

Intermediate 40B: 3-(2-(4-Hydroxy-phenyl)-pyridin-4-yl)-2-(3-chloro-phenyl)-imidazo[1,2-a]pyridine



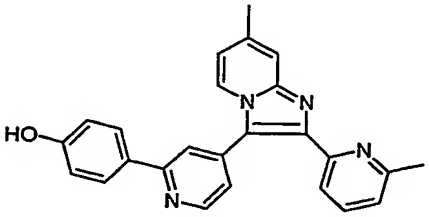
Intermediate 28B (3g, 7.83 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]- dioxaborolan-2-yl)-phenol (Aldrich, 2.24g, 10.2 mmol) were coupled and treated as described for intermediate 30B to afford, after chromatography on silicagel (DCM/MeOH 95:5), the title compound (1.6g, 51%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 9.05 (s, 1H), 8.55 (d, 1H), 7.95 (d, 1H), 7.6 (m, 3H), 7.5 (m, 2H), 7.25 (m, 1H), 7.1 (m, 4H), 6.7 (m, 3H).

Intermediate 41B: 8-Methyl-3-(2-(4-hydroxy-phenyl)-pyridin-4-yl)-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



Intermediate 27B (2.06g, 5.45 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-phenol (Aldrich, 1.56g, 7.08 mmol) were coupled and treated as described for intermediate 30B to afford the title compound as a brown powder (0.865g, 40%); [APCI MS] m/z 393 MH^+.

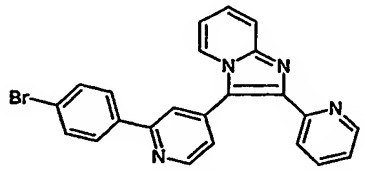
Intermediate 42B: 7-Methyl-3-(2-(4-hydroxy-phenyl)-pyridin-4-yl)-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



Intermediate 26B (1.17g, 3.1 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]- dioxaborolan-2-yl)-phenol (Aldrich, 0.55g, 4.02 mmol) were coupled and treated as described for

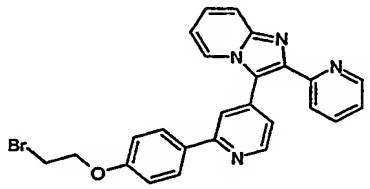
intermediate 30B to afford the title compound (0.932g, 77%); [APCI MS] m/z 393 MH^+.

Intermediate 43B: 3-(2-(4-Bromo-phenyl)-pyridin-4-yl)-2-(pyridin-2-yl)-imidazo[1,2-a]pyridine



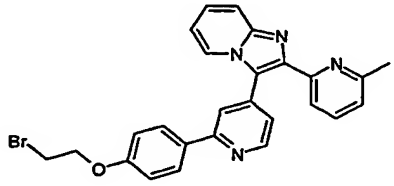
Intermediate 21B (3 g, 8.55 mmol) and 4-bromophenyl boronic acid (Aldrich, 2.23 g, 11.11 mmol) were coupled and treated as described for intermediate 30B to afford, after chromatograhy on silica gel (DCM/MeOH 98/2 then 95: 5), the title compound as an oil (2.9 g, 79.5%); [APCI MS] m/z: 428.2 (MH+).

Intermediate 44B: 3-{2-[4-(2-Bromo-ethoxy)-phenyl]-pyridin-4-yl}-2-pyridin-2-yl-imidazo[1,2-*a*]pyridine



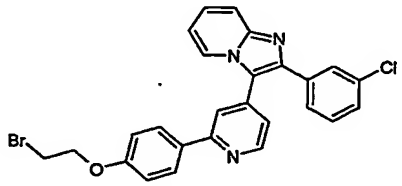
To a solution of intermediate 38B (0.38 g, 1.04 mmol) in acetone (20 ml) was added cesium carbonate (0.68 g, 2.08 mmol) and 1,2-dibromoethane (0.9 ml, 10.4 mmol). The reaction was heated under reflux for 2 days. After cooling, the reaction was filtered and the solvent was removed in vacuo. Purification by chromatography on silica gel (DCM/MeOH, 90/10) gave the title compound (140 mg, 28%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 8.78 (d, 1H), 8.49 (d, 1H), 8.14 (d, 1H), 7.93 (m, 4H), 7.72 (t, 2H), 7.34 (m, 2H), 7.17 (m, 1H), 7.00 (d, 2H), 6.83 (t, 1H), 4.33 (t, 2H), 3.65 (t, 3H).

Intermediate 45B: 3-{2-[4-(2-Bromo-ethoxy)-phenyl]-pyridin-4-yl}-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-*a*]pyridine



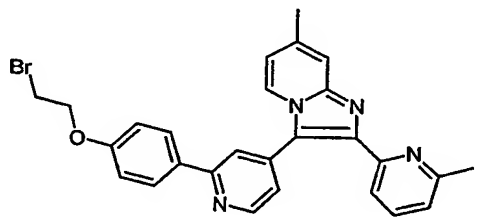
Intermediate 39B (0.46 g, 1.22 mmol) and 1,2-dibromoethane (2.08 ml, 24.32 mmol) were reacted as described for intermediate 44B to afford, after purification by chromatography on silica gel (DCM/MeOH, 95/5), the title compound (300 mg, 50%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 8.75 (d, 1H), 8.15 (d, 1H), 7.93 (m, 3H), 7.71 (t, 2H), 7.56 (t, 2H), 7.35 (d, 1H), 7.26 (m, 1H), 7.00 (m, 3H), 6.82 (t, 1H), 4.33 (t, 2H), 3.65 (t, 2H), 2.37 (s, 3H).

Intermediate 46B: 3-{2-[4-(2-Bromo-ethoxy)-phenyl]-pyridin-4-yl}-2-(6-chloro-phenyl)-imidazo[1,2-*a*]pyridine



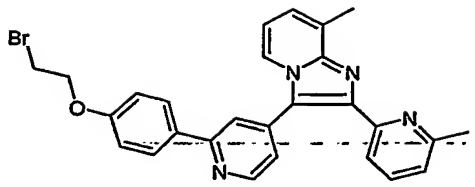
Intermediate 40B (1.6 g, 4 mmol) and 1,2-dibromoethane (4.37 ml, 50 mmol) were reacted and treated as described for intermediate 44B to afford, after purification by chromatography on silica gel (DCM/MeOH, 95/5), the title compound as an orange oil (2.98g, 100%); [APCI MS] m/z 505 MH^+.

Intermediate 47B: 7-Methyl-3-{2-[4-(2-bromo-ethoxy)-phenyl]-pyridin-4-yl}-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-*a*]pyridine



Intermediate 42B (3.72g, 9.49 mmol) and 1,2-dibromoethane (8.2 ml, 94.88 mmol) were reacted and treated as described for intermediate 44B to afford after purification by chromatography on silica gel (DCM/MeOH, 95/5) and trituration with pentane, the title compound as a yellow powder (1.28g, 27%); [APCI MS] m/z 500 MH^+.

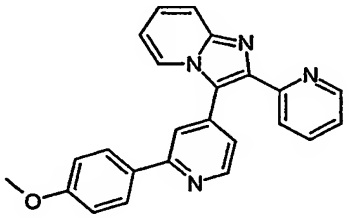
Intermediate 48B: 8-Methyl-3-{2-[4-(2-bromo-ethoxy)-phenyl]-pyridin-4-yl}-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-*a*]pyridine



Intermediate 41B (0.865g, 2.2 mmol) and 1,2-dibromoethane (1.9 ml, 22.06 mmol) were reacted and treated as described for intermediate 44B to afford after purification by chromatography on silica gel (DCM/MeOH, 95/5), the title compound (0.389g, 35%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 8.75 (d, 1H), 8.05 (d, 1H), 7.95 (s, 1H), 7.9 (d, 2H), 7.7 (d, 1H), 7.55 (t, 1H), 7.35 (d, 1H), 7 (m, 2H), 6.9 (d, 2H), 6.75 (t, 1H), 4.35 (t, 2H), 3.65 (t, 2H), 2.75 (s, 3H), 2.35 (s, 3H).

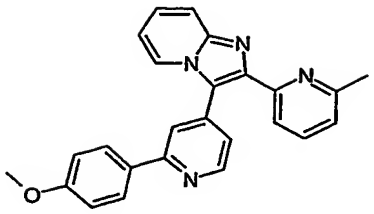
Examples

Example 1B : 3-[2-(4-Methoxyphenyl)-pyridin-4-yl]-2-pyridin-2-yl-imidazo[1,2-*a*]pyridine



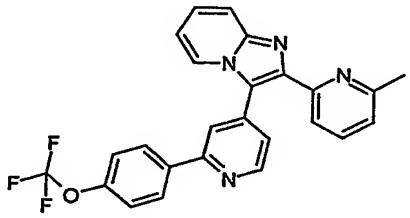
A solution of intermediate 21B (500mg, 1.42 mmol) in toluene (10 ml) was treated with tetrakis triphenylphosphine palladium(0) (ACROS, 165mg , 10%mol) and stirred at room temperature for 30 min. Aquesous Na_2CO_3 (2M, 0.6 ml) was added to the reaction mixture, followed by 4-methoxyphenyl boronic acid (ALDRICH, 282mg, 1.3eq, 1.85 mmol) and the mixture was heated under reflux overnight. The cooled mixture was poured into ice and extracted with toluene. The layers were separated and the organic layer was washed with water, dried over Na_2SO_4 and filtered. Evaporation of the filtrate *in vacuo* gave a crude oil which was purified by chromatography on silica gel (DCM/MeOH, 90/10) to give the title compound (68mg, 13%); m.p. 222°C; [LCTof] $C_{24}H_{18}N_4O$ (MH+) calculated 379.1559 (MH+) found 379.1540 -5.1ppm.

Example 2B : 3-[2-(4-methoxy-phenyl)-pyridin-4-yl]-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



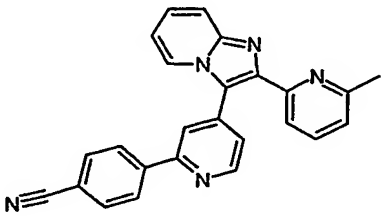
Intermediate 22B (300mg, 0.82mmol) and 4-methoxy-phenyl boronic acid (ALDRICH, 162mg, 1.07mmol) were coupled and treated as described for example 1 to afford, after purification by chromatography on silica gel (DCM/MeOH, 95/5), the title product as a yellow powder (112mg, 35%); m.p:174°C; [APCI MS] m/z 393 (MH^+).

Example 3B : 2-(6-methyl-pyridin-2-yl)-3-[2-(4-trifluoromethoxy-phenyl)-pyridin-4-yl]-imidazo[1,2-a]pyridine



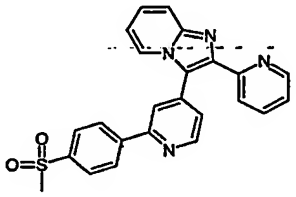
Intermediate 22B (300mg, 0.82mmol) and 4-trifluoromethoxy-benzene boronic acid (LANCASTER, 220mg, 1.07mmol) were coupled and treated as described for example 1B to afford, after precipitation in pentane, the title product (137mg, 37%); m.p. 120°C; [APCI MS] m/z 447 (MH^+).

Example 4B: 3-[2-(4-Cyano-phenyl)-pyridin-4-yl]-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



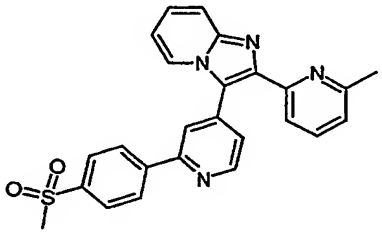
Intermediate 22 (300mg, 0.82mmol) and 4-cyanobenzene boronic acid (LANCASTER, 157mg, 1.07mmol) were coupled and treated as described for example 1B to afford, after recrystallisation from ethyl acetate, the title compound as a yellow powder (31mg, 10%); m.p. 214°C; [APCI MS] m/z 388 (MH^+).

Example 5B: 3-[2-(4-Methanesulfonyl-phenyl)-pyridin-4-yl]-2-pyridin-2-yl-imidazo[1,2-a]pyridine



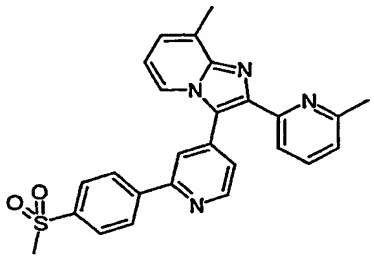
Intermediate 21B (1.5g, 4.3mmol) and 4-(methanesulfonyl)-phenyl boronic acid (1g, 5.1mmol) were coupled and treated as described for example 1B to afford, after crystallisation in acetonitrile, the title compound as a pink powder (730mg, 40.33%); m.p. 242-244°C; [APCI MS] m/z 427 (MH+).

Example 6B: 3-[2-(4-Methanesulfonyl-phenyl)-pyridin-4-yl]-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



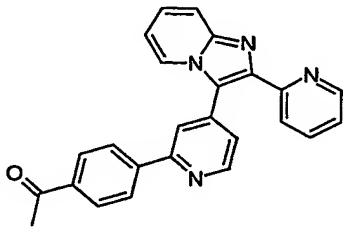
Intermediate 22B (300mg, 0.82mmol) and 4-(methanesulfonyl)-phenyl boronic acid (FRONTIER, 214mg, 1.06mmol) were coupled and treated as described for example 1B to afford, after purification by chromatography on silica gel (DCM/MeOH, 95/5), the title compound as a yellow foam (121mg, 33%); [APCI MS] m/z 441 (MH+); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.85 (d, 1H) ; 8.2 (d, 1H); 8.14 (d, 1H); 8.09 (m, 3H); 7.82 (d, 1H); 7.74 (d,1H); 7.58 (m, 2H); 7.53 (m, 1H); 7.44(dd, 1H); 7.3 (t, 1H) ; 7.05 (d,1H) ; 6.85 (t, 1H) ; 3.09 (s, 3H) ; 2.31 (s, 1H).

Example 7B: 8-Methyl-2-(6-methyl-pyridin-2-yl)-3-[2-[4-(methylsulfonyl)phenyl]-pyridin-4-yl]-imidazo[1,2-a]pyridine



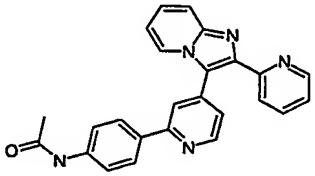
Intermediate 27B (0.5g, 1.3 mmol) and 4-(methylsulfonyl)phenyl boronic acid (0.344g, 1.72 mmol) were coupled and treated as described for example 1B to afford, after trituration with ethyle acetate, the title compound as a yellow gummy solid (250mg, 41%); [APCI MS] m/z 455 MH^+; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.85 (d, 1H), 8.2 (d, 2H), 8.05 (m, 3H), 7.85 (d, 1H), 7.5 (m, 3H), 7.1 (m, 2H), 6.8 (t, 1H), 3.1 (s, 3H), 2.75 (s, 3H), 2.35 (s, 3H).

Example 8B: 3-[2-(4-(Acetyl)phenyl)-pyridin-4-yl]-2-(pyridin-2-yl)-imidazo[1,2-a]pyridine



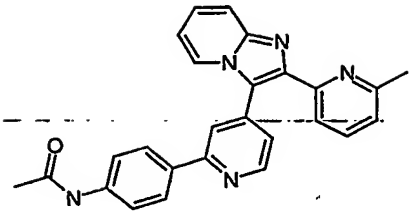
Intermediate 21B (2.1g, 5.98 mmol) and 4-(acetyl)phenyl boronic acid (1.27g, 7.77 mmol) were coupled and treated as described for example 1B to afford, after trituration with ethyl acetate, the title compound as a cream solid (1.9g, 81.4%); m.p. 214°C; [APCI MS] m/z 391.22 (MH^+).

Example 9B: 3-[2-(4-(Methylcarbonylamino)phenyl)-pyridin-4-yl]-2-pyridin-2-yl-imidazo[1,2-a]pyridine



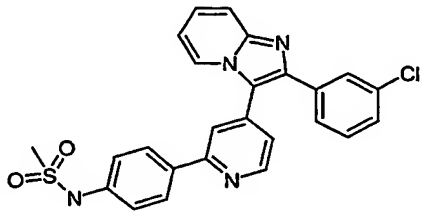
Intermediate 21B (0.3g, 0.85mmol) and 4'-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-acetanilide (0.29 g, 1.11 mmol) were coupled and treated as described for example 1B to afford the title compound as a yellow powder (283mg, 82%); m.p. 133°C; [APCI MS] m/z 406 (MH+).

Example 10B : 3-[2-(4-(methylcarbonylamino)phenyl)-pyridin-4-yl]-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



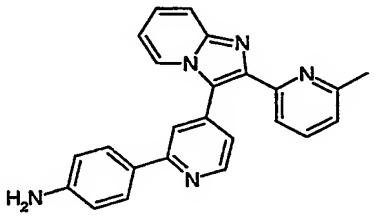
Intermediate 22B (3.76g, 10.32mmol) and 4'-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-acetanilide (3.5g, 13.42 mmol) were coupled and treated as described for example 1B to afford, after crystallisation from DCM, the title compound as a creme powder (2.34g, 54%); m.p. 257°C; [LCTof] $C_{26}H_{21}N_5O$ (MH+) calculated 420.1824 (MH+) found 420.1808 -3.8ppm.

Example 11B : 2-(3-chloro-phenyl)-3-[2-(4-(methanesulfonylamino)phenyl)-pyridin-4-yl]- imidazo[1,2-a]pyridine



Intermediate 28B (300mg, 0.78mmol) and intermediate 12 (302mg, 1.02 mmol) were coupled and treated as described for example 1B to afford, after purification by flash chromatography on silica gel (DCM/MeOH, 95/5), the title compound as a yellow foam (93mg, 25%); m.p. 60°C (become gummy); [LCTof] $C_{25}H_{19}ClN_4O_2S$ (MH+) calculated 475.0995 (MH+) found 475.0975 -4.2ppm.

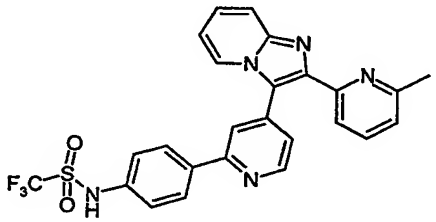
Example 12B: 2-(6-methyl-pyridin-2-yl)-3-{2-[4-amino-phenyl]-pyridin-4-yl}-imidazo[1,2-a]pyridine



A mixture of example 10B (2.3g, 5.48 mmol) in MeOH (50 ml) and 1N HCl (50 ml) were stirred at room temperature for 18 hours. The mixture was then basified with 1N NaOH and then extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and the fitrate concentrated under reduced pressure to give the title compound as a yellow solid (0.79g, 38%); [APCI MS] m/z: 378 MH^+; ^1H NMR (300

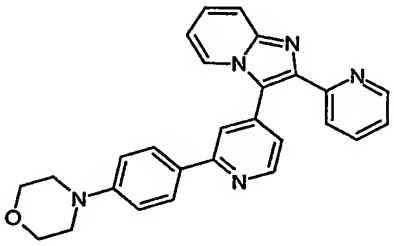
MHz, $CDCl_3$) δ ppm: 8.7 (d, 1H), 8.1 (d, 1H), 7.85 (m, 3H), 7.7 (d, 1H), 7.6 (d, 1H), 7.45 (t, 1H), 7.25 (m, 2H), 7 (d, 1H), 6.8 (t, 1H), 6.7 (d, 2H), 3.85 (m, 2H), 2.4 (s, 3H).

Example 13B: 2-(6-Methyl-pyridin-2-yl)-3-{2-[4-(trifluoromethylsulfonylamino)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



To a solution of example 12B (390mg, 1.03mmol) in DCM (10ml) were added trifluoromethanesulfonic anhydride (0.2ml, 8.55mmol) and triethylamine (0.17 ml, 1.24 mmol) and the mixture was stirred at room temperature for 3 days. The mixture was poured into water and extracted with DCM. The layers were separated and the organic phases combined, dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with DCM/MeOH (9/1) to give the title compound (178mg, 33.8%); m.p. 135°C; [LCTof] $C_{25}H_{18}F_3N_5O_2S_1$ 510.1212 (MH^+) calculated 510.1229 (MH^+) found 3.4ppm.

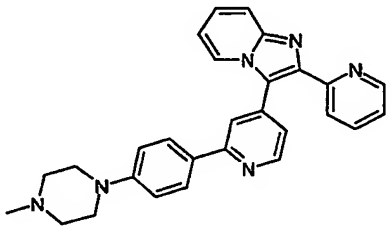
Example 14B : 3-[2-(4-(morpholin-4-yl)-phenyl)-pyridin-4-yl]-2-pyridin-2-yl-imidazo[1,2-a]pyridine



A mixture of intermediate 43B (400 mg, 0.93 mmol), morpholine (1.2 eq, 0.1 ml, 1.1 mmol), $Pd_2(dba)_3$ (0.05 eq, 43 mg, 0.05 mmol), BINAP (0.15 eq, 88 mg, 0.14 mmol) and potassium *tert*-butoxide (1.4 eq, 126 mg, 1.31 mmol) in toluene (50 ml) was heated under reflux for 2 hours. The reaction mixture was extracted between DCM and water and combined organic extracts were dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with DCM/MeOH (98/2, 95/5 and then 93/7).

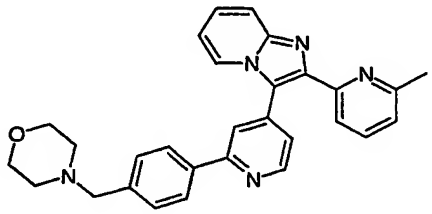
The resulting oil was crystallised from DCM/pentane to give the title compound as a yellow solid (140 mg, 35%); m.p. 145°C (become gummy); [LCTof] $C_{27}H_{23}N_5O$ (MH+) calculated 434.1981 (MH+) found 434.1993 2.8ppm.

Example 15B: 3-{2-[4-(4-Methylpiperazin-1-yl)-phenyl]-pyridin-4-yl}-2-pyridin-2-yl-imidazo[1,2-a]pyridine



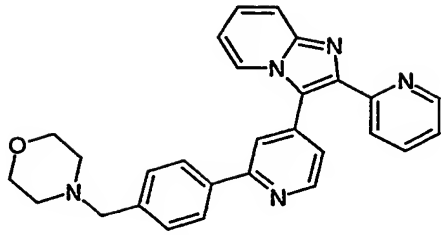
Intermediate 43B (400mg, 0.94mmol) and *N*-methyl-piperazine (0.125 ml, 1.2eq, 1.13 mmol) were coupled and treated as described for example 14B to afford, after crystallisation in DCM/diisopropylether, the title compound (70mg, 17%); m.p. 150°C (become gummy); APCI MS] m/z 447 (MH+).

Example 16B: 2-(6-Methyl-pyridin-2-yl)-3-[2-(4-(morpholin-4-ylmethyl)phenyl)-pyridin-4-yl]-imidazo[1,2-a]pyridine



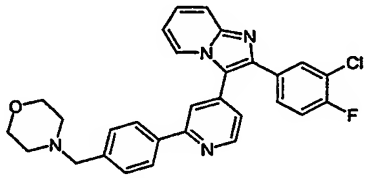
To a solution of intermediate 30B (310mg, 0.79mmol) and morpholine (1.5 eq, 0.1ml, 1.2mmol) in dry dichloroethane (30ml) was added sodium triacetoxyborohydride (1.5eq, 253mg, 1.2 mmol) and the mixture stirred for 3 hours at room temperature. The mixture was basified with 1N NaOH, and the aqueous layer was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated. The concentrate was recrystallised from ethyl acetate to give the title compound as a white powder (194mg, 53%); m.p. 156°C; [APCI MS] m/z 462.28 (MH+).

Example 17B: 3-[2-(4-(Morpholin-4-yl-methyl)-phenyl)-pyridin-4-yl]-2-pyridin-2-yl-imidazo[1,2-a]pyridine



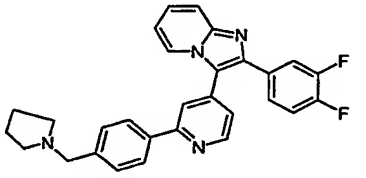
Intermediate 31B (1.1g, 2.9mmol) and morpholine (307µl, 3.5mmol) were coupled and treated as described for example 16B to afford, after purification by chromatography on silica gel (DCM/MeOH, 90/10), the title compound as a powder (1.1g, 85%); m.p. 80°C (degradation); [APCI MS] m/z 448 (MH^+).

Example 18B: 2-(3-Chloro-4-fluoro-phenyl)-3-[2-(4-(morpholin-4-yl-methyl)phenyl)-pyridin-4-yl]-imidazo[1,2-a]pyridine



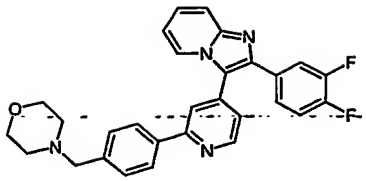
Intermediate 32B (0.35g, 0.82mmol) and morpholine (0.107ml, 1.5 eq, 1.23 mmol) were coupled and treated as described for example 16B to afford, after crystallisation from AcOEt/iPr_2O, the title compound (45 mg, 11%); m.p. 189°C; [APCI MS] m/z 499 (MH+).

Example 19B: 2-(3,4-Difluoro-phenyl)-3-[2-(4-(pyrrolidin-1-yl-methyl)phenyl)-pyridin-4-yl]-imidazo[1,2-a]pyridine



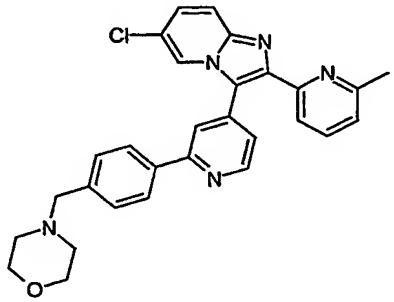
Intermediate 33B (0.30g, 0.73mmol) and pyrrolidine (0.09ml, 1.5 eq, 1.1 mmol) were coupled and treated as described for example 16B to afford, after crystallisation from DCM/pentane, the title compound as a yellow powder (51 mg, 45%); m.p. 155°C; [LCTof] $C_{29}H_{24}F_2N_4$ (MH+) calculated 467.2047 (MH+) found 467.2063 3.4ppm.

Example 20B: 2-(3,4-Difluoro-phenyl)-3-[2-(4-(morpholin-1-yl-methyl)phenyl)-pyridin-4-yl]-imidazo[1,2-a]pyridine



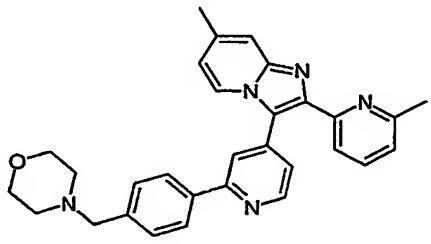
Intermediate 33B (0.30g, 0.73mmol) and morpholine (0.095mL, 1.1 mmol) were coupled and treated as described for example 16B to afford, after crystallisation from DCM/pentane, the title compound as a white powder (135 mg, 38%); m.p. 205°C; [LCTof] $C_{29}H_{24}F_2N_4O$ (MH+) calculated 483.1996 (MH+) found 483.2030 7.1ppm.

Example 21B : 6-Chloro-2-(6-methyl-pyridin-2-yl)-3-[2-(4-(morpholin-4-yl-methyl)phenyl)-pyridin-4-yl]-imidazo[1,2-*a*]pyridine



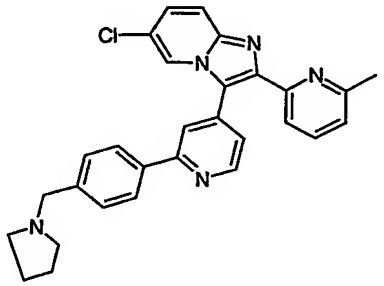
Intermediate 34B (0.40g, 0.94mmol) and morpholine (0.123 ml, 1.41 mmol) were coupled and treated as described for example 16B to afford, after crystallisation from diethyl ether, the title compound (129 mg, 28%); m.p. 157°C; [APCI MS] m/z 496 (MH^+).

Example 22B: 7-Methyl-2-(6-methyl-pyridin-2-yl)-3-[2-(4-(morpholin-4-yl-methyl)phenyl)-pyridin-4-yl]-imidazo[1,2-*a*]pyridine



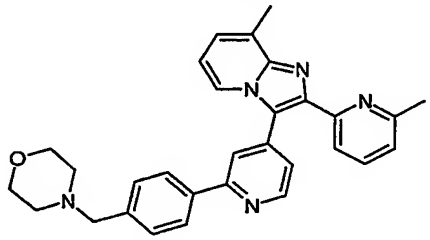
Intermediate 35B (270 mg, 0.66 mmol) and morpholine (0.09 ml, 1 mmol) were coupled and treated as described for example 16B to afford, after crystallisation from AcOEt, the title compound as an orange solid (68 mg, 22%); m.p. 188°C; [LCTof] $C_{30}H_{29}N_5O$ (MH+) calculated 476.2450 (MH+) found 476.2445 -1ppm.

Example 23B: 6-Chloro-2-(6-methyl-pyridin-2-yl)-3-[2-(4-(pyrrolidin-1-yl-methyl)phenyl)-pyridin-4-yl]-imidazo[1,2-*a*]pyridine



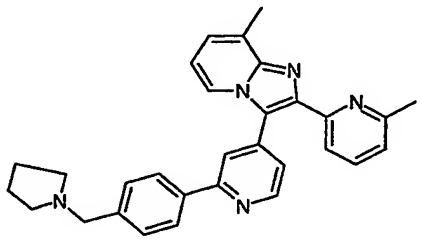
Intermediate 34B (0.30g, 0.7mmol) and pyrrolidine (0.09 ml, 1.06 mmol) were coupled and treated as described for example 16B to afford, after purification by chromatography on silica gel eluting with DCM/MeOH (90/10 then 80/20), the title compound as a white powder (122 mg, 36%); m.p. 134°C; [LCTof] $C_{29}H_{26}ClN_5$ (MH+) calculated 480.1955 (MH+) found 480.1900 -6.9ppm.

Example 24B: 8-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-((morpholin-4-yl)methyl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



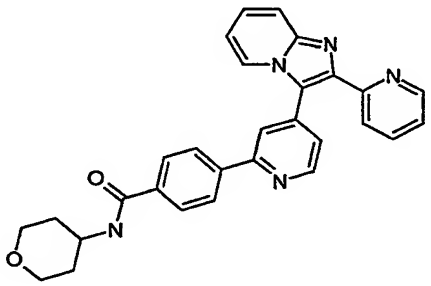
Intermediate 36B (400mg, 0.99 mmol) and morpholine (0.13ml, 1.49 mmol) were coupled and treated as described for example 16B to afford, after trituration with DCM/pentane, the title compound as a white solid (198mg, 42.13%); m.p. 122°C; [APCI MS] m/z 476 MH^+.

Example 25B: 8-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-((pyrrolidin-1-yl)methyl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine, hydrochloride



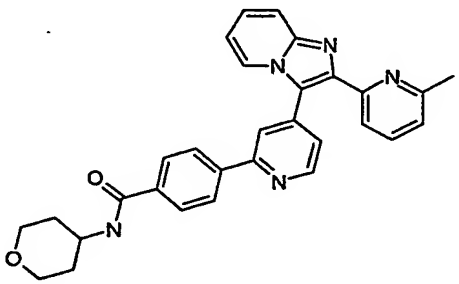
To a solution of intermediate 36B (400mg, 0.99mmol) in DCM (20ml) were added pyrrolidine (0.13ml, 1.49mmol) and sodium triacetoxyborohydride (315mg, 1.49mmol) and the mixture was stirred at room temperature for 24 hours. The mixture was poured into water and extracted with DCM. The layers were separated and the combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM and a solution of hydrochloric acid in diethyl ether (1N, 1.3 ml, 1.3mmol) was added. The resulting precipitate was filtered, washed with diisopropyle oxyde and dried to give the title compound as a yellow solid (322mg, 71%); m.p. 197°C; ^{1}H NMR (300 MHz, DMSO) δ ppm: 8.95 (d, 1H), 8.45 (m, 2H), 8.2 (d, 2H), 7.95 (t, 1H), 7.8 (d, 2H), 7.75 (m, 3H), 7.5 (d, 1H), 7.25 (t, 1H), 4.4 (m, 2H), 3.3 (m, 2H), 3.05 (m, 2H), 2.95 (s, 3H), 2.5 (s, 3H), 2.05 (m, 2H), 1.9 (m, 2H).

Example 26B: 3-[2-(4-((Tetrahydropyran-4-yl)aminocarbonyl)phenyl)-pyridin-4-yl]-2-pyridin-2-yl-imidazo[1,2-a]pyridine



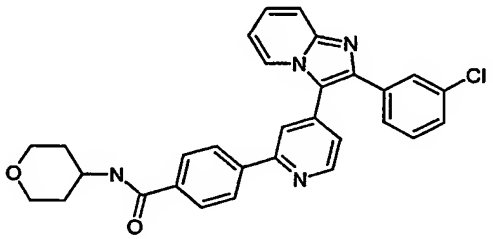
Intermediate 21B (224mg, 0.638 mmol) and intermediate 10B (206mg, 0.83 mmol) were coupled and treated as described for example 1B to afford, after purification by chromatography on silica gel (DCM/MeOH 90/10), the title compound as a yellow powder (57mg, 19%); m.p. 179°C; [APCI MS] m/z 476 (MH+).

Example 27B: 3-[2-(4-((tetrahydropyran-4-yl)aminocarbonyl)phenyl)-pyridin-4-yl]-2-(6-methyl-pyridin-2-yl)-imidazo[1,2-a]pyridine



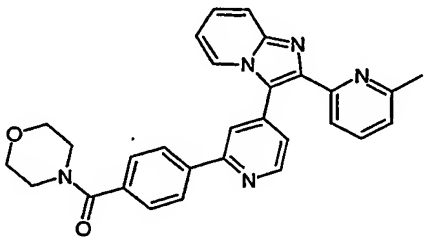
Intermediate 22B (300mg, 0.82 mmol) and intermediate 10B (266mg, 1.07 mmol) were coupled and treated as described for example 1B to afford, after purification by chromatography on silica gel (DCM/MeOH, 90/10), the title compound as a yellow powder (37mg, 9%); m.p. 128°C; [APCI MS] m/z 490 (MH+).

Example 28B: 2-(3-Chloro-phenyl)-3-[2-(4-((tetrahydropyran-4-yl)aminocarbonyl)phenyl)-pyridin-4-yl]- imidazo[1,2-a]pyridine



Intermediate 28B (300mg, 0.78mmol) and intermediate 10B (253mg, 1.02 mmol) were coupled and treated as described for example 1B to afford, after purification by preparative plate chromatography on silica gel (DCM/MeOH 90/10), the title compound as a yellow powder (51mg, 13%); m.p. 234°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.85 (d, 2H), 7.75 (d, 2H), 7.65 to 7.55 (m, 4H), 7.45 to 7.35 (m, 6H), 7.2 (m, 1H), 6 (d, 1H), 4.2 (m, 1H), 4 (m, 2H), 3.5 (m, 2H), 2 (m, 2H), 1.6 (m, 2H).

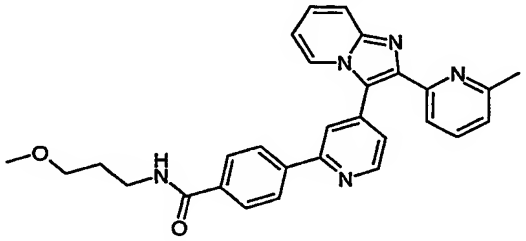
Example 29B: 2-(6-Methyl-pyridin-2-yl)-3-{2-[4-((morpholin-4-yl)carbonyl)phenyl]-pyridin-4-yl}-imidazo[1,2-a]pyridine



To a solution of intermediate 37B (500mg, 1.23mmol) in DMF (30ml) were added morpholine (0.13ml, 1.48mmol), HOBT (200mg, 1.48mmol), EDCI (283mg, 1.48mmol) and triethylamine (0.2ml; 1.48mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was extracted between DCM and 1N sodium hydroxide solution. The layers were separated and the organic phase was wahed with water. The layers were separated and the orgainic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with DCM/MeOH (95/5)

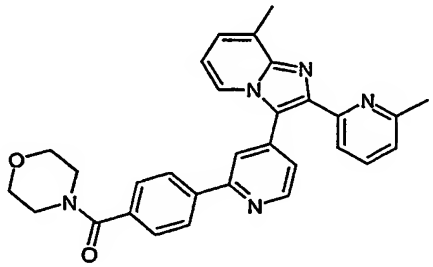
to give (after trituration with diisopropyl ether) the title compound as a pale yellow solid (147mg, 25.13%); m.p. 110°C; [APCI MS] m/z 476.33 (MH+).

Example 30B: 2-(6-Methyl-pyridin-2-yl)-3-{2-[4-((3-methoxypropylamino)carbonyl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



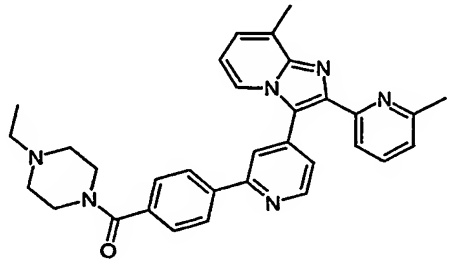
Intermediate 37B (400mg, 0.98mmol) and 3-methoxypropylamine (0.11ml, 1.18mmol) were coupled and treated as described for example 29B to afford, after trituration with DCM/pentane, the title compound as a pale yellow solid (210mg, 44.69%); m.p. 165°C; [APCI MS] m/z 478.36 (MH^+).

Example 31B: 8-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-((morpholin-4-yl)carbonyl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



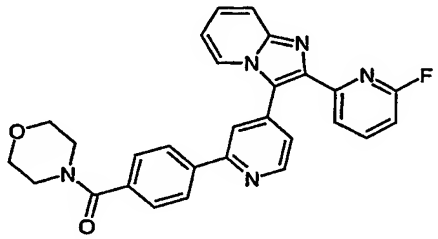
Intermediate 27B (500mg, 1.32mmol) and intermediate 12B (545mg, 1.72mmol) were coupled and treated as described for example 1B to afford the title compound as a yellow oil (543mg, 84%); [APCI MS] m/z 490 (MH+).

Example 32B: 8-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-((1-ethyl-piperazin-4-yl)carbonyl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



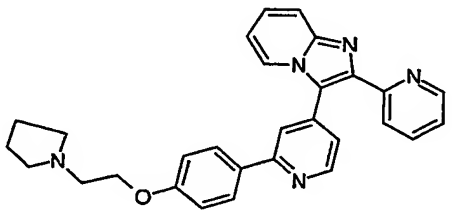
Intermediate 27B (500mg, 1.32mmol) and intermediate 13B (591mg, 1.72mmol) were coupled and treated as described for example 1B to afford the title compound (316mg, 46%); m.p. 212°C; [LCTof] $C_{32}H_{32}N_6O$ 517.2715 (MH^+) calculated 517.2751(MH^+) found 7ppm.

Example 33B: 2-(6-Fluoro-pyridin-2-yl)-3-{2-[4-((morpholiny-4-yl)carbonyl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



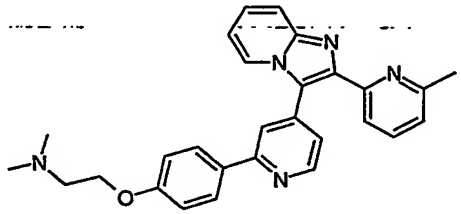
Intermediate 29B (200mg, 0.54mmol) and intermediate 12B (224mg, 0.7mmol) were coupled and treated as described for example 1B to afford the title compound as a white solid (30mg, 12%); m.p. 191°C; [LCTof] $C_{28}H_{22}N_5O_2F_1$ 480.1836 (MH^+) calculated 480.1756 (MH^+) found -16ppm.

Example 34B: 2-(Pyridin-2-yl)-3-{2-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



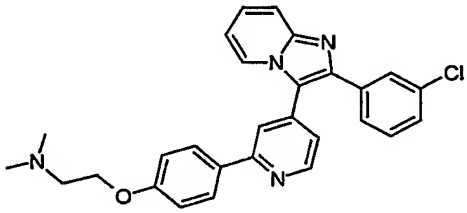
A solution of intermediate 44B (140 mg, 0.3mmol) and pyrrolidine (0.75ml, 9 mmol) in EtOH (5 ml) was heated under reflux for 6 days. After cooling water was added and the product was extracted with DCM. The organic phase was dried over Na_2SO_4, filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by chromatography on silica gel eluting with DCM/MeOH/TEA (80/20/1%) to give the title compound (13 mg, 10%); [APCI MS] m/z 462 (MH+); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.75 (d, 1H), 8.5 (d, 1H), 8.15 (d, 1H), 7.9 (m, 3H), 7.85 (s, 1H) , 7.7 (m, 2H), 7.3 (m, 2H), 7.2 (m, 1H), 7 (d, 2H), 6.85 (t, 1H), 4.2 (t, 2H), 3 (t, 2H), 2.75 (m, 4H), 1.85 (m, 4H).

Example 35B: 2-(6-Methyl-pyridin-2-yl)-3-{2-[4-(2-(dimethylamino)ethoxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



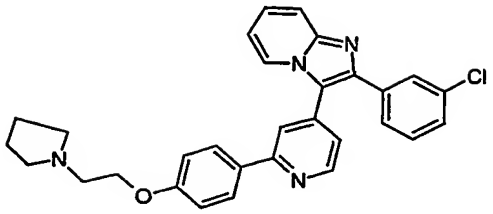
A solution of intermediate 45B (300 mg, 6.2 mmol) and dimethylamine (solution 40% in water, 2ml) in THF (2ml) was stirred at room temperature during 18 hours. After cooling water was added and the product was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered off and the solvent was removed under reduced pressure to give the title compound as a orange gum (135 mg, 48%); [APCI MS] m/z 450 (MH+); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.8 (d, 1H), 8.2 (d, 1H), 7.95 (m, 3H), 7.75 (m, 2H), 7.6 (t, 1H), 7.4 (d, 1H), 7.3 (m, 1H), 7.05 (m, 3H), 6.9 (t, 1H), 4.25 (t, 2H), 3 (t, 2H), 2.55 (s, 6H), 2.4 (s, 3H).

Example 36B: 2-(3-Chloro-phenyl)-3-{2-[4-(2-(dimethylamino)ethoxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



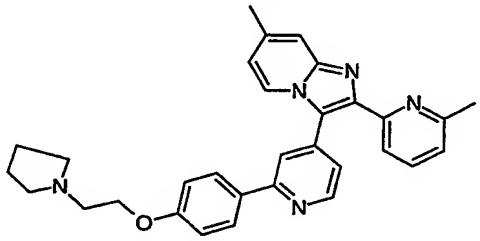
Intermediate 46B (300 mg, 0.6 mmol) and dimethylamine (solution 40% in water, 2ml) were coupled and treated as described for example 35B to afford, after purification by chromatography on silica gel eluting with DCM/MeOH (90/10 then 80/20), the title compound as a yellow gum (98 mg, 35%); [LCTof] $C_{28}H_{25}ClN_4O$ (MH+) calculated 469.1795 (MH+) found 469.1723 -15ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.8 (d, 1H), 8.1 (d, 1H), 7.9 (d, 2H), 7.8 (s, 1H), 7.7 (m, 2H), 7.45 (d, 1H), 7.25 (m, 3H), 7.2 (m, 1H), 7 (d, 2H), 6.85 (t, 1H), 4.35 (t, 2H), 3.25 (t, 2H), 2.7 (s, 6H).

Example 37B: 2-(3-Chloro-phenyl)-3-{2-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



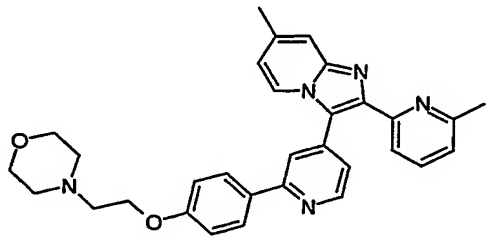
Intermediate 46B (300mg, 0.59mmol) and pyrrolidine (0.5ml, 5.96mmol) were coupled and treated as described for example 34B to afford, after trituration with pentane, the title compound as a pale yellow solid (80mg, 27.1%); m.p. 298°C; [LCTof] $C_{30}H_{27}ClN_4O$ 495.1952 (MH+) calculated 495.1957(MH+) found 1ppm.

Example 38B: 7-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



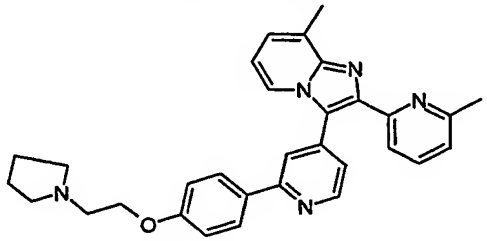
Intermediate 47B (426mg, 0.85mmol) and pyrrolidine (0.71ml, 8.55mmol) were coupled and treated as described for example 34B to afford, after trituration with pentane, the title compound as a pale yellow solid (102mg, 24.4%); m.p. 163°C; [LCTof] $C_{31}H_{31}N_5O_1$ 490.2607 (MH^+) calculated 490.2600 (MH^+) found –1.4ppm.

Example 39B: 7-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-(2-(morpholin-4-yl)ethoxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



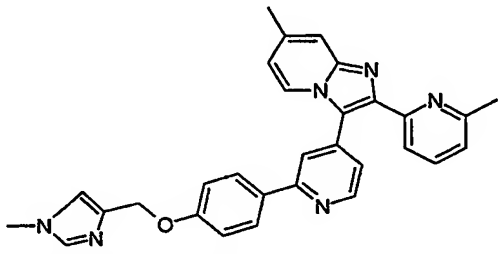
Intermediate 47B (426mg, 0.85mmol) and morpholine (0.74ml, 8.55mmol) were coupled and treated as described for example 34B to afford the title compound as an orange foam (357mg, 82.64%); [LCTof] $C_{31}H_{31}N_5O_2$ 506.2556 (MH^+) calculated 506.2534 (MH^+) found 4.4ppm; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.8 (d, 1H), 8.05 (d, 1H), 7.9 (m, 3H), 7.7 (d, 1H), 7.6 (t, 1H), 7.5 (s, 1H), 7.35 (d, 1H), 7 (m, 3H), 6.7 (d, 1H), 4.2 (t, 2H), 3.8 (m, 4H), 2.85 (t, 2H), 2.6 (m, 4H), 2.45 (s, 3H), 2.4 (s, 3H).

Example 40B: 8-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-(2-(pyrrolidin-1-yl)ethoxy))phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



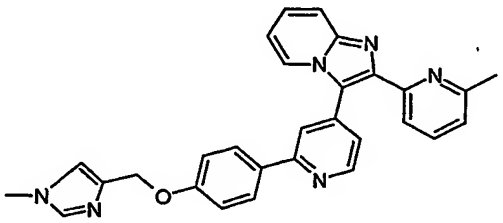
Intermediate 48B (389mg, 0.78mmol) and pyrrolidine (0.65ml, 7.8mmol) were coupled and treated as described for example 34B to afford the title compound as a gummy solid (160mg, 41.9%); [APCI MS] m/z 490 (MH+); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.75 (d, 1H), 8.05 (d, 1H), 7.9 (m, 3H), 7.7 (d, 1H), 7.55 (t, 1H), 7.3 (d, 1H), 7.05 (m, 2H), 6.95 (d, 2H), 6.7 (t, 1H), 4.25 (t, 2H), 3.05 (t, 2H), 2.9 (m, 4H), 2.7 (s, 3H), 2.4 (s, 3H), 1.95 (m, 4H).

Example 41B: 7-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-((1-methyl-imidazol-4-yl)methyloxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



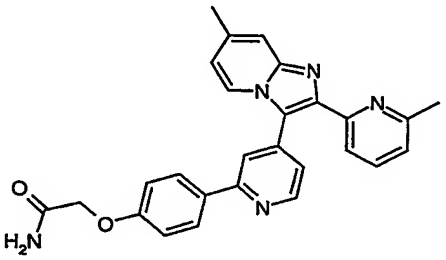
To a solution of intermediate 42B (400mg, 1.02mmol) in DMF (20ml) was added portionwise sodium hydride (60% in mineral oil, 101mg, 2.55mmol) and the mixture was stirred at room temperature for 20 minutes. Intermediate 7B (173mg, 1.32mmol) was then added and the mixture was heated at 60°C for 3 days. The reaction mixture was poured into water and extracted with DCM. The combined organic extracts were separated, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with DCM/MeOH (9/1), to give (after trituration with diisopropyl ether), the title compound as a yellow solid (130mg, 26%); m.p. 217°C; [LCTof] $C_{30}H_{26}N_6O_1$ 487.2246 (MH^+) calculated 487.2247 (MH^+) found 0.2ppm.

Example 42B: 2-(6-Methyl-pyridin-2-yl)-3-{2-[4-((1-methyl-imidazol-4-yl)methyloxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



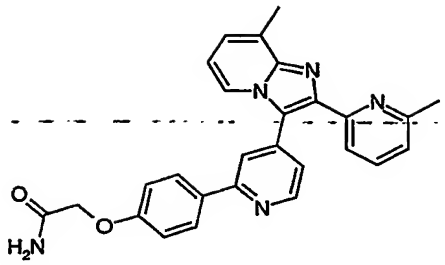
Intermediate 39B (400mg, 1.06mmol) and intermediate 7B (212mg, 1.27mmol) were coupled and treated as described for example 41B to afford, after trituration with diisopropyl ether, the title compound as a white solid (200mg, 40%); m.p. 120°C; [APCI MS] m/z 473 (MH+).

Example 43B: 7-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4(aminocarbonylmethyloxy)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



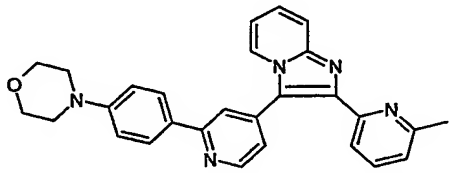
To a solution of intermediate 42B (500mg, 1.27mmol) in acetone (25ml) were added caesium carbonate (623mg, 1.91mmol) and bromoacetamide (264mg, 1.91mmol) and the mixture was heated under reflux for 48 hours. On cooling, the reaction mixture was extracted between water and DCM. The layers were separated and the combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with DCM/MeOH (95/5), to give (after trituration with pentane/ethyle acetate), the title compound (133mg, 23%); m.p. 213°C; [APCI MS] m/z 450 MH^+.

Example 44B: 8-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-(aminocarbonylmethyloxyl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



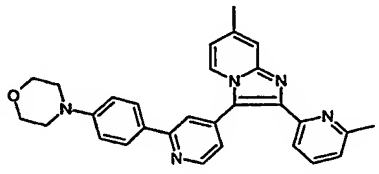
Intermediate 41B (500mg, 1.27mmol) and bromoacetamide (264mg, 1.91mmol) were coupled and treated as described for example 43B to afford, after trituration with diisopropyl ether, the title compound (80mg, 14%); m.p. 183°C; [APCI MS] m/z 450 (MH+).

Example 45B: 2-(6-Methyl-pyridin-2-yl)-3-{2-[4-(morpholin-4-yl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



To a solution of intermediate 20B (3g, 8.04mmol) in DCM (80 ml) was added bromine-polymer-supported (Fluka, 5.03g, 8.04 mmol) and the suspension was stirred at room temperature for 3 hours. The suspension was filtered, washing the resin with ethanol. 2-Aminopyridine (ALDRICH, 1.51g , 16.08 mmol) was added to the combined filtrate and washings and the mixture was heated at reflux for 18 hours. On cooling, the residue was extracted between water and DCM. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The concentrate was purified by chromatography on silica gel (eluting with DCM/MeOH, 98/2 then 95/5) to give (after trituration with diisopropyl ether, the title compound (1.2g; 33.38%); m.p. 190 °C; [LCTof] $C_{28}H_{25}N_5O_1$ 448.2137 (MH^+) calculated 448.2081 (MH^+) found -12.5ppm.

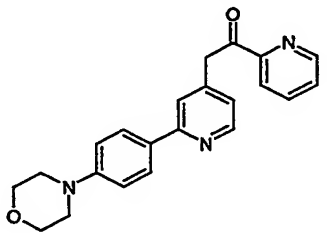
Example 46B: 7-Methyl-2-(6-methyl-pyridin-2-yl)-3-{2-[4-(morpholin-4-yl)phenyl]-pyridin-4-yl}-imidazo[1,2-*a*]pyridine



Intermediate 20B (1.27g, 3.4 mmol) was reacted as described for example 45B, to afford after trituration with diisopropyl ether, the title compound (0.6g, 38.22%); m.p. 208°C; [LCTof] $C_{29}H_{27}N_5O_1$ 462.2294 (MH^+) calculated 462.2263 (MH^+) found -6.7ppm.

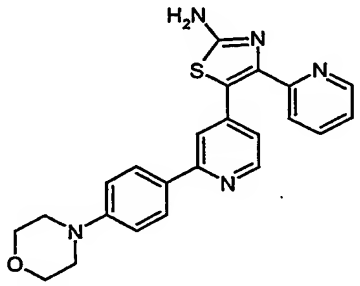
Experimental for thiazoles (C)

Intermediate 1C: 2-[2-(4-(morpholin-4-yl)phenyl)-pyridin-4-yl]-1-pyridin-2-yl-ethanone



The title compound was obtained as an orange oil (1.42 g, 38.64%), by reacting intermediate 14B and intermediate 9B as described for intermediate 20B; ^1H NMR (300MHz, $CDCl_3$) δ ppm: 8.7 (d, 1H), 8.55 (d, 1H), 8.05 (d, 1H), 7.9 (d, 2H), 7.8 (m, 1H), 7.5 (m, 1H), 7.15 (m, 1H), 6.95 (m, 3H), 4.55 (s, 2H), 3.85 (m, 4H), 3.2 (m, 4H).

Example 1C: 5-{2-[4-(Morpholin-4-yl)phenyl]pyridin-4-yl}-4-pyridin-2-yl-1,3-thiazol-2-amine

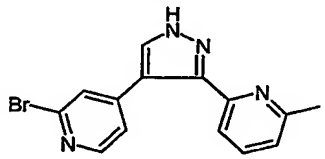


To a solution of Intermediate 1C (0.4 g, 1.11 mmol) in CH_2Cl_2 (20 ml) was added polymer-supported pyridinium perbromide (Aldrich, 1eq, 1.11 mmol) and the suspension shaken for 50 min. The resin was removed by filtration, with the filtrate being added directly to thiourea (0.25 g, 3 eq, 3.33 mmol) and the resin washed many times with ethanol. The filtrate was heated at reflux overnight, allowed to cool and concentrated. The residue was basified with aqueous NaOH, extracted into CH_2Cl_2.and this phase washed with water. The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. After chromatography on silicagel (CH_2Cl_2/MeOH, 95/5 then 90/10) and crystallisation from ethyl acetate, the

titled compound was obtained as cream crystals (108 mg, 23.35%); m.p. 246°C; MS(API): 416(MH+).

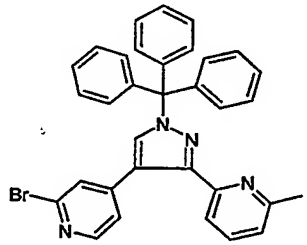
Experimental for pyrazoles (D)

Intermediate 1D: 2-Bromo-4-(3-(6-methyl-pyridin-2-yl)-1H-pyrazol-4-yl)pyridine



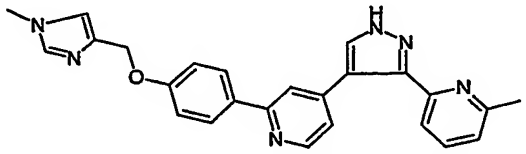
A solution of intermediate 1A (5.84 g, 20 mmol) in dry DMF (20 ml) under nitrogen was treated with glacial acetic acid (2.4eq, 2.76 ml) over 2 min. DMF.DMA (1.5eq., 4 ml) was added dropwise and the mixture stirred at room temperature under nitrogen for 1h. Hydrazine monohydrate (7.5eq, 91 ml, 1.876 mol) was added dropwise at room temperature and the resulting mixture heated at 50°C for 3 h. The reaction mixture was poured into water (300ml) and extracted with CH_2Cl_2 . The organic phases were combined, dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to afford a brown oil which after purification by chromatography on silica gel (eluent : CH_2Cl_2/CH_3OH 98:2) gave the title compound as a yellow solid (3.07 g, 49%); [APCI MS] m/z 315 (MH+).

Intermediate 2D: 2-bromo-4-[3-(6-methylpyridin-2-yl)-1-trityl-1*H*-pyrazol-4-yl]pyridine



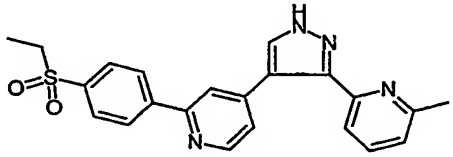
Intermediate 1D (3.07 g , 9.8 mmol) and trityl chloride (1.5 eq, 4.1 g, 14.7 mmol) were reacted with potassium carbonate (3eq, 29.4mmol) in acetone (100ml). The reaction mixture was subsequently heated to reflux and stirred for 24 hours. The reaction mixture was filtered, the filtrate concentrated, and then partitioned between CH_2Cl_2 and H_2O. The organic phase was dried over Na_2SO_4 and concentrated. The resulting crude material was purified by flash chromatography on silica gel, eluting with CH_2Cl_2/MeOH (98:2) to give to afford the title compound as the major isomer of a mixture of the two isomers , as a light yellow solid (4.9 g, 90%); [APCI MS] m/z: 558 (MH+).

Example 1D: 2-{4-(1-Methyl-imidazol-4-yl)methyloxy]-phenyl}-4-(3-(6-methyl-pyridin-2-yl)-1H-pyrazol-4-yl)pyridine



To a solution of intermediate 2D (4 g, 7 mmol) in DMF (80 ml) cooled in an ice bath, was added portionwise sodium hydride (0.6g, 3 eq, 21 mmol) and the mixture then stirred at room temperature for 30 mins. 4-Chloromethyl-1-methyl-imidazole, hydrochloride (1.6 g, 10 mmol) was added and the mixture stirred at room temperature overnight and then poured into water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave a crude oil which was purified by chromatography on silica gel (CH_2Cl_2/MeOH 97:3) to give the trityl compound as an oil (3 g). This compound was dissolved in methanol (60 ml) and HCl (1N, 40 ml) and the solution was heated under reflux for 2 hours and then concentrated *in vacuo*. The residue was dissolved in water and washed with CH_2Cl_2. The aqueous layer was basified with NaOH (1N) and extracted with CH_2Cl_2. The organic extract was washed with water and dried over Na_2SO_4, filtered and evaporated to give a solid which was crystallised from EtOH to give the title compound as white crystals (1.1 g, 37%); m.p. 191°C; LCTof : $C_{25}H_{22}N_6O$: calculated : 423.1933, found : 423.1928 1.2ppm.

Example 2D: 2-[4-(Ethylsulfonyl)phenyl]-4-[3-(6-methyl-pyridin-2-yl)-1H-pyrazol-4-yl]pyridine



To a solution of intermediate 2D (0.5 g, 0.9 mmol) in DME (18 ml) and water (9 ml) was added 4-(ethylsulfonyl)phenyl boronic acid (1.3 eq, 0.25 g, 1.17 mmol), tetrakis triphenylphosphine palladium (0.05 g) and Na_2CO_3 (3 eq, 0.28g, 2.69 mmol) and the mixture heated under reflux overnight. The cooled mixture was poured into ice and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave an oil which was dissolved in

MeOH (30 ml) and HCl (1N, 20 ml). The solution was heated under reflux during 3 hours and then concentrated under reduced pressure. The residue was dissolved in water and washed with CH_2Cl_2. The aqueous layer was basified with NaOH (1N) and extracted with CH_2Cl_2. The organic extract was washed with water and dried over Na_2SO_4, filtered and evaporated under reduced pressure. After chromatography on silica gel (CH_2Cl_2/MeOH, 95/5) and crystallisation from DMF, the title compound was obtained as white crystals (166 mg, 45.7%); [APCI MS m/z 405 (MH+); m.p. 244°C.

Experimental for triazoles (E)

Intermediate 1E: 2-Chloro-4-iodo-pyridine

To a ice-cooled solution of 4-amino-2-chloro-pyridine (8.09g, 63 mmol, 1eq) in water (150mL) was added concentrated 98% HCl whilst maintaining the reaction at 0°C. A solution of sodium nitrite (5.65g, 82mmol, 1.3eq) in water (50mL) was added slowly at –10°C. The mixture was stirred at -10°C for 40 min and a solution of potassium iodide (12.55g, 75.6mmol, 1.2eq) in water (50mL) was added. The resulting mixture was stirred at 0°C overnight. After treatment with NaOH 35%, and extraction with ethyl acetate, the organic phases were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (eluent: CH_2Cl_2 then CH_2Cl_2/ CH_3OH 99/1) to give the title compound as an orange solid (9.5g, 63%); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (1H, d), 7.68 (1H, s), 7.52 (1H, d); (GC-MS) m/z: 239.

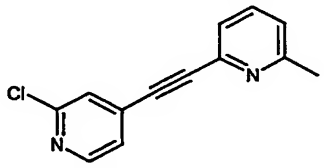
Intermediate 2E : 2-Methyl-6-trimethylsilanylethynyl-pyridine

To a solution of 2-bromo-4-methyl-pyridine (25g, 0.15 mol) in dry THF (200mL), were added TMEDA (200mL) and TMS-acetylene (100mL, excess) under N_2. The resulting mixture was degassed with nitrogen for 10 min, then tetrakis(triphenlyphosphine) palladium(0) (3.7mmol, 4.3g) and copper iodide (14.7mmol, 2.8g) were added. The resulting mixture was heated at 60°C for 18h. The reaction mixture was concentrated and the residue partitioned between ethyl acetate / water. The organic phase was dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave a crude product which was purified by chromatography on silica gel (CH_2Cl_2) to give the title compound (18.4g, 65%) as a black oil; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 7.58-7.49 (1H, m), 7.30 (1H, d), 7.10 (1H, d), 2.56 (3H, s), 0.28 (9H, s).

Intermediate 3E : 2-Ethynyl-6-methyl-pyridine

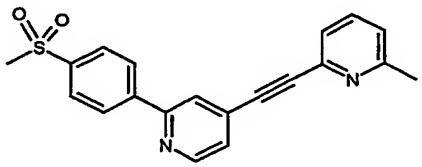
To a solution of Intermediate 2E (18.4g, 0.097mol) in MeOH (100 ml) was added potassium carbonate (4eq, 0.39mol, 53.7g). The reaction mixture was then stirred at room temperature for 30 min and the solvent evaporated to dryness. The residue was partitioned between ethyl acetate / water. The organic layer was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure to give the title compound (8.75g, 77%) as a brown oil; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.34 (1H, m), 7.14 (1H, d), 6.98 (1H, d), 2.97 (1H, s), 2.40 (3H, s).

Intermediate 4E : 6-Methyl-2-[(2-chloro-pyridin-4-yl)-ethynyl]-pyridine



To a solution of intermediate 1E (1.85g, 7.74mmol) in dry THF (40mL) were added under nitrogen, TMEDA (20mL) and intermediate 3E (1.1eq, 1g, 8.51mmol). The resulting mixture was degassed with nitrogen for 10 mins, then tetrakis(triphenlyphosphine) palladium(0) (0.464mmol, 537mg) and copper iodide (0.928 mmol, 177mg) were added. The resulting mixture was heated at 60°C for 4h. The mixture was poured into a saturated solution of NH_4Cl and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc 90:10) to afford the title compound as a beige solid (1.54g, 86.4%); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.29 (1H, d), 7.52 (1H, t), 7.39 (1H, s), 7.34-7.24 (2H, m), 7.10 (1H, d), 2.50 (3H, s).

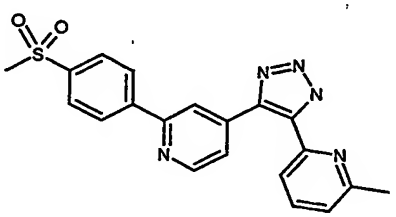
Intermediate 5E: 2-[(2-(4-methylsulfonylphenyl)-pyridin-4-yl)-ethynyl]-6-methyl-pyridine



Intermediate 4E (1g, 4.37mmol) and 4-(methylsulfonyl)phenyl boronic acid (1.14g, 5.7 mmol), were dissolved in a mixture of toluene (30mL) and EtOH (10mL). To this solution were added tetrakis(triphenlyphosphine) palladium(0) (0.118 g, 0.1mmol) and aqueous sodium carbonate 2M (8.6mL, 17.2mmol) under nitrogen. The resulting

mixture was stirred under reflux for 6 h. The mixture was hydrolysed with water and extracted with ethyl acetate, the combined organic phases were washed with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude product which was purified by chromatography on silica gel (eluent : CH_2Cl_2/CH_3OH 98:2) to give the title compound as a yellow oil (0.7g, 46%); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.66 (1H, d), 8.14 (2H, d), 7.98 (2H, d), 7.90 (1H, s), 7.56 (1H, t), 7.43-7.32 (2H, m), 7.12 (1H, d), 3.03 (3H, s), 2.50 (3H, s); [APCI MS] m/z : 349 (MH^+).

Example 1E : 2-(4-Methanesulfonyl-phenyl)-4-(5-(6-methyl)-pyridin-2-yl-1H-[1,2,3]triazol-4-yl)-pyridine



To a solution of Intermediate 5E (700mg, 2 mmol) in dry DMF (13 ml) was added azidotrimethylsilane (8 mmol, 930mg). The reaction mixture was then stirred at 100°C overnight. The reaction mixture was hydrolysed with water and extracted with CH_2Cl_2 . The organic phase was washed with water, dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave a crude product which was purified by chromatography on silica gel (toluene / isopropylamine 95:5). The crude oil was precipitated in a mixture CH_2Cl_2/hexane to give the title compound as a yellow powder (260mg, 33.2%); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.70 (1H, d), 8.28 (1H, s), 8.15 (2H, d), 7.95 (2H, d), 7.70-7.57 (2H, m), 7.50 (1H, d), 7.15 (1H, d), 3.00 (3H, s), 2.50 (3H, s), NH triazole not observed; Calcd. Mass for $C_{20}H_{17}N_5O_2S$ (MH+):392.1181. Found (H.R.M.S): 392.1218.

Biology

The biological activity of the compounds of the invention may be assessed using the following assays:

Assay 1 (Cellular transcriptional assay)

The potential for compounds of the invention to inhibit TGF- β signaling may be demonstrated, for example, using the following in vitro assay.

The assay was performed in HepG2 cells stably transfected with the PAI-1 promoter (known to be a strong TGF-β responsive promoter) linked to a luciferase (firefly) reporter gene. The compounds were selected on their ability to inhibit luciferase activity in cells exposed to TGF-β. In addition, cells were transfected with a second luciferase (Renilla) gene which was not driven by a TGF-β responsive promoter and was used as a toxicity control.

96 well microplates were seeded, using a multidrop apparatus, with the stably transfected cell line at a concentration of 35000 cells per well in 200 µl of serum-containing medium. These plates were placed in a cell incubator.

18 to 24 hours later (Day 2), cell-incubation procedure was launched. Cells were incubated with TGF-β and a candidate compound at concentrations in the range 50 nM to 10 µM (final concentration of DMSO 1%). The final concentration of TGF-β (rhTGFβ-1) used in the test was 1 ng/mL. Cells were incubated with a candidate compound 15-30 mins prior to the addition of TGF-β. The final volume of the test reaction was 150 µl. Each well contained only one candidate compound and its effect on the PAI-1 promoter was monitored.

Columns 11 and 12 were employed as controls. Column 11 contained 8 wells in which the cells were incubated in the presence of TGF-β, without a candidate compound. Column 11 was used to determine the 'reference TGF-β induced firefly luciferase value' against which values measured in the test wells (to quantify inhibitory activity) were compared. In wells A12 to D12, cells were grown in medium without TGF-β. The firefly luciferase values obtained from these positions are representative of the 'basal firefly luciferase activity'. In wells E12 to H12, cells were incubated in the presence of TGF-β and 500 µM CPO (Cyclopentenone, Sigma), a cell toxic compound. The toxicity was revealed by decreased firefly and renilla luciferase activities (around 50 % of those obtained in column 11).

12 to 18 hours later (day 3), the luciferase quantification procedure was launched. The following reactions were performed using reagents obtained from a Dual Luciferase Assay Kit (Promega). Cells were washed and lysed with the addition of 10 µl of passive lysis buffer (Promega). Following agitation (15 to 30 mins), luciferase activities of the plates were read in a dual-injector luminometer (BMG lumistar). For

this purpose, 50 µl of luciferase assay reagent and 50 µl of 'Stop & Glo' buffer were injected sequentially to quantify the activities of both luciferases. Data obtained from the measurements were processed and analysed using suitable software. The mean Luciferase activity value obtained in wells A11 to H11 (Column 11, TGF-βonly) was considered to represent 100% and values obtained in wells A12 to D12 (cells in medium alone) gave a basal level (0%). For each of the compounds tested, a concentration response curve was constructed from which an IC_{50} value was determined graphically.

Assay 2 (Alk5 Fluorescence Polarization Assay)

Kinase inhibitor compounds conjugated to fluorophores, can be used as fluorescent ligands to monitor ATP competitive binding of other compounds to a given kinase. The increase in depolarization of plane polarized light, caused by release of the bound ligand into solution, is measured as a polarization/anisotropy value. This protocol details the use of a rhodamine green-labelled ligand for assays using recombinant GST-ALK5 (residues 198-503).

Assay buffer components: 62.5 mM Hepes pH 7.5 (Sigma H-4034), 1 mM DTT (Sigma D-0632), 12.5 mM $MgCl_2$ (Sigma M-9272), 1.25 mM CHAPS (Sigma C-3023).

Protocol: Solid compound stocks were dissolved in 100% DMSO to a concentration of 1 mM and transferred into column 1, rows A-H of a 96-well, U bottom, polypropylene plate (Costar #3365) to make a compound plate. The compounds were serially diluted (3-fold in 100% DMSO) across the plate to column 11 to yield 11 concentrations for each test compound. Column 12 contained only DMSO. A Rapidplate™-96 was used to transfer 1 µl of sample from each well into a 96-well, black, U-bottom, non-treated plate (Costar #3792) to create an assay plate.

ALK5 was added to assay buffer containing the above components and 1 nM of the rhodamine green-labelled ligand so that the final ALK5 concentration was 10 nM based on active site titration of the enzyme. The enzyme/ligand reagent (39 µl) was added to each well of the previously prepared assay plates. A control compound (1 µl) was added to column 12, rows E-H for the low control values. The plates were read immediately on a LJL Acquest fluorescence reader (Molecular Devices, serial number AQ1048) with excitation, emission, and dichroic filters of 485nm, 530 nm, and 505 nm, respectively. The fluorescence polarization for each well was

calculated by the Acquest reader and then imported into curve fitting software for construction of concentration response curves. The normalized response was determined relative to the high controls (1 µl DMSO in column 12, rows A-D) and the low controls (1 µl of control compound in column 12, rows E-H). An IC_{50} value was then calculated for each compound

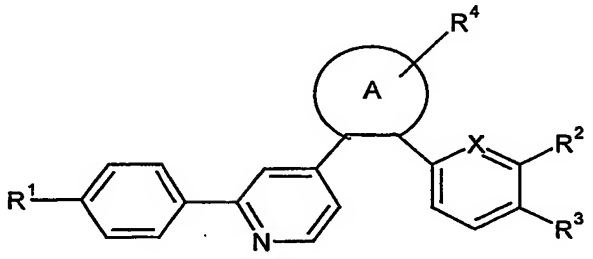
Using the above assays all Examples of the invention show ALK5 receptor modulator activity (having IC_{50} values in the range of 1 to 100nM) and TGF-β cellular activity (having IC_{50} values in the range of 0.001 to 10µM).

4-{4-[4-(2-*tert*-Butyl-5-{6-methyl}-pyridin-2-yl-1*H*-imidazol-4-yl)-pyridin-2-yl]-phenyl}-morpholine (Example 6A) showed an ALK5 receptor modulator activity of 34 nM and TGF-β cellular activity of 183 nM.

N-(tetrahydropyran-4-yl)-4-(4-{2-isopropyl-5-[6-methyl-pyridin-2-yl]-1*H*-imidazol-4-yl}-pyridin-2-yl)-benzamide (Example 15A) showed an ALK5 receptor modulator activity of 25 nM and TGF-β cellular activity of <14 nM.

Claims

1. A compound of formula (I), a pharmaceutically acceptable salt, solvate or derivative thereof;



(I)

wherein

A is selected from the list: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, indazole, imidazopyridine, quinazoline, quinoline, isoquinoline, pyrazole and triazole;

X is N or CH;

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo, cyano, perfluoro C_{1-6}alkyl, perfluoroC_{1-6}alkoxy, $-NR^5R^6$, $-(CH_2)_nNR^5R^6$, $-O(CH_2)_nOR^7$, $-O(CH_2)_n$-Het, $-O(CH_2)_nNR^5R^6$, $-CONR^5R^6$, $-CO(CH_2)_nNR^5R^6$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NR^5SO_2R^7$, $-NR^5COR^7$ and $-O(CH_2)_nCONR^5R^6$;

R^2 is selected from hydrogen, C_{1-6}alkyl, halo, cyano or perfluoroC_{1-6}alkyl;

R^3 is selected from hydrogen or halo;

R^4 is selected from hydrogen, halo, phenyl, C_{1-6}alkyl or $-NR^5R^6$;

where

R^5 and R^6 are independently selected from hydrogen; C_{1-6}alkyl optionally substituted by amino, monoC_{1-6}alkylamino, diC_{1-6}alkylamino, Het, alkoxy or cyano; Het; and C_{3-6}cycloalkyl optionally substituted by C_{1-6}alkyl; or R^5 and R^6 together with the nitrogen atom to which they are attached form a 3, 4, 5, 6 or 7-membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more

substituents selected from halo (such as fluoro, chloro, bromo), cyano, $-CF_3$, hydroxy, $-OCF_3$, C_{1-6}alkyl and C_{1-6}alkoxy;

R^7 is selected from hydrogen and C_{1-6}alkyl;

Het is a 5 or 6-membered heterocyclyl group which may be saturated, unsaturated or aromatic, which may contain one or more heteroatoms selected from N, S or O and which may be substitued by C_{1-6}alkyl; and

n is 1-4;

with the provisos that :

a) when A is thiazole (wherein the thiazole sulfur is on the same side as the 4-pyridyl moiety); X is N; R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, cyano, perfluoroC_{1-6}alkyl or perfluoroC_{1-6}alkoxy; R^2 is hydrogen, C_{1-6}alkyl, halo, cyano or perfluoroC_{1-6}alkyl; and R^3 is hydrogen or halo; then R^4 is not NH_2;

b) when X is N, A is pyrazole (where the ring containing X is attached to the pyrazole ring at the carbon atom next to a pyrazole ring nitrogen) and R^2 is hydrogen, then R^3 is not hydrogen.

2 A pharmaceutical composition comprising a compound defined in claim 1 and a pharmaceutically acceptable carrier or diluent.

3 The use of a compound defined in claim 1 in the manufacture of a medicament for the treatment or prophylaxis of a disorder characterised by the overexpression of TGF-β.

4 The use of a compound defined in claim 1 in the manufacture of a medicament for the treatment or prophylaxis of a disorder mediated by the ALK5 receptor in mammals.

5 The use according to claim 4 wherein the disorder is selected from chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis, kidney fibrosis, liver fibrosis [for example, hepatitis B virus (HBV), hepatitis C virus (HCV)], alcohol induced hepatitis, retroperitoneal fibrosis,

mesenteric fibrosis, haemochromatosis and primary biliary cirrhosis, endometriosis, keloids and restenosis.

6 The use according to claim 5 wherein the disorder is kidney fibrosis.

5

7 A compound defined in claim 1 for use as a medicament.

Abstract

This invention relates to novel heterocyclyl pyridine derivatives which are inhibitors of the transforming growth factor, ("TGF")-ß signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF-β type I or activin-like kinase ("ALK")-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway.